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Extrarenal determinants of kidney filter function

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Abstract

The kidney is an organ involved in cross talk with many human organs. The link between the immune system and the kidney has been studied in some detail, although data precisely elucidating their interaction are sparse, in particular with regard to the function of the kidney filter apparatus. Current research suggests that an understanding of the impairment of this cross talk between the bone marrow, as a fundament of the immune system and the kidney will provide meaningful insights into the pathophysiological mechanisms of impaired kidney filter function. Circulating factors have long been implicated in the pathogenesis of idiopathic nephrotic syndrome, particularly focal segmental glomerulosclerosis (FSGS) and its recurrence. Soluble urokinase receptor (suPAR) has emerged as a circulating factor responsible for FSGS and also as an early predictive marker for the development of various renal diseases. The bone marrow has recently been revealed as a predominant source of suPAR with deleterious effects on the kidney filter. These new findings have led to bone marrow or hematopoietic stem cell transplants being considered as potential therapeutic options for preventing the post-transplantation recurrence of FSGS or even as a treatment for the original disease associated with high suPAR levels. Whereas bone marrow transplantation for patients with preexisting chronic kidney disease is challenging, recent clinical trials have demonstrated the promising outcome of combined bone marrow and kidney transplantation in patients with kidney failure. In this review, with its brief update on suPAR, we describe the critical new role of the bone marrow in the pathogenesis of the kidney disease process and the functional connection between these two organs through the soluble mediator, suPAR. We also comment on the feasibility of bone marrow transplants for the treatment of patients with chronic renal failure arising from recurrent FSGS.

Keywords

suPAR; Bone marrow; FSGS recurrence; Nephrotic syndrome; Chronic kidney disease

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Compliance with ethical standards

Disclosures All authors equally contributed to the creation of this manuscript.

J.R. is given as inventor on pending and issued patents relating to anti-proteinuric therapies. He stands to gain royalties from present and future commercialization. J.R. is also co-founder and advisor to TRISAQ, a biotechnology company. The remaining authors report no conflicts of interest.

Idiopathic nephrotic syndrome and focal segmental glomerulosclerosis

Nephrotic syndrome develops when damage has occurred to the glomeruli, the structural units in the kidneys that work to filter the blood. This damage to the glomerular filtration barrier allows protein leakage into the urine, causing increased excretion of protein (proteinuria).

Nephrotic syndrome may develop not only as a consequence of identified causes such as infections, toxic drugs, or systemic diseases (e.g., diabetes, amyloidosis and lupus erythematosus; SLE) but also as a result of unknown (idiopathic) causes including minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and membranous nephropathy (MN). About 80% of patients with idiopathic nephrotic syndrome are sensitive to steroids and other immunosuppressive agents such as cyclosporine, mycophenolate mofetil, or cyclophosphamide and show the remission of proteinuria. The remaining 20% of patients are resistant to the immunosuppressive treatment and eventually progress to end-stage renal disease (ESRD), requiring either dialysis or kidney transplantation.

FSGS is the most common primary glomerular disease leading to ESRD in the United States (Cravedi et al. 2013). The recurrence of FSGS occurs frequently (up to 50%) and rapidly (within hours to days) after kidney transplantation and is associated with renal dysfunction and frequent allograft loss (Kitiyakara et al. 2004; Ponticelli and Glassock 2010). The risk factors for recurrence of FSGS include younger age at onset (especially under the age of 6 years), non-African background, rapid progression from onset to ESRD (within 3 years), heavy proteinuria before transplantation and loss of previous allograft because of recurrence (up to 100%, on average 90%; Newstead 2003; Vinai et al. 2010). Notably, recurrence generally occurs in patients with primary FSGS, whereas the risk of recurrence is very low in familial/genetic FSGS and secondary FSGS (Maas et al. 2013; Newstead 2003).

Circulating factors

Although the etiology of FSGS is unknown, mounting evidence has strongly supported the hypothesis of a circulating factor causing primary FSGS and its recurrence. First, rapid or even immediate recurrence of FSGS following kidney transplantation favors the presence of a circulating factor (Vincenti and Ghiggeri 2005). Second, the complete resolution of allograft dysfunction after re-transplantation of an organ initially affected by recurrent FSGS in a recipient without FSGS as a native disease (Gallon et al. 2012) supports the hypothesis that a circulating factor is detrimental to the glomerular filtration barrier, particularly to podocytes and that podocyte injury before scar formation is reversible. In agreement with the assumption of a circulating permeable factor that causes FSGS and that might be removed by plasmapheresis (PP, also known as plasma exchange [PE]) or immunoadsorption, previous studies have shown the efficacy of these procedures in inducing the remission of proteinuria and in improving renal function in patients with recurrent FSGS (Artero et al. 1994; Kaplan-Pavlovic et al. 2002), preferably in conjunction with high dose cyclosporine A or cyclophosphamide (Weber and Tonshoff 2005). A systemic review by Ponticelli has shown that PP induces partial or complete remission in 70% of children and 63% of adults

with recurrent FSGS (Ponticelli and Glassock 2010). Even preemptive PP (prior to kidney transplantation) may reduce the risk of recurrent FSGS (Gohh et al. 2005; Ohta et al. 2001).

In agreement with these clinical observations, experimental studies have shown that the plasma of patients with recurrent FSGS provokes proteinuria in rats (Sharma et al. 1999, 2002; Zimmerman 1984) and increased albumin permeability in isolated glomeruli (Savin et al. 1996). In an animal model of FSGS, Buffalo/Mna rats, in which proteinuria spontaneously develops with a histological pattern similar to that of human FSGS (Kato and Watanabe 1983; Nakamura et al. 1986), the authors demonstrated a causal role of circulating factors in the recurrence of FSGS (Le Berre et al. 2002). As seen in humans, immunosuppressive treatments such as glucocorticoids, cyclosporine, or cyclophosphamide reduced proteinuria in these Buffalo/Mna rats. When Buffalo/Mna recipient rats receive healthy donor kidneys, proteinuria relapses. Conversely, when Buffalo/Mna kidneys are transplanted into healthy recipient rats, proteinuria and renal lesions are resolved. This study supports the notion that host circulating factor(s) is/are responsible for recurrence of FSGS.

Several factors have been proposed as the circulating factors responsible for primary FSGS, including cardiotrophin-like cytokine-1 (CLC-1; McCarthy et al. 2010), soluble urokinase type plasminogen receptor (suPAR; Wei et al. 2011), vasodilator-stimulated phosphoprotein (VASP; Harris et al. 2013) and anti-CD40 antibodies (Delville et al. 2014). To date, the most intensively studied factor is suPAR. The role of suPAR in recurrent FSGS has been confirmed by two completely independent research groups (Huang et al. 2013; Wei et al. 2012).

suPAR

suPAR is a soluble (circulating) form of urokinase plasminogen activator receptor (uPAR), a glycosylphosphatidylinositol (GPI)-anchored three-domain protein (Blasi and Carmeliet 2002; Thuno et al. 2009). This receptor exists in multiple forms because of alternative splicing, protein glycosylation and enzymatic cleavage of the mature protein (Smith and Marshall 2009) and has been linked to the activation of the immune system and cancer. It first emerged as a direct pathogenic molecule in FSGS (Wei et al. 2011). Our previous reports demonstrated that suPAR binds to and activates $\beta 3$ integrin on podocytes, leading to podocyte foot process effacement and disruption of the glomerular barrier function with proteinuria (Wei et al. 2008). Studies have shown that PP induces clinical remission and decreases serum suPAR levels in patients with FSGS (Staeck et al. 2015; Wei et al. 2011). However, further human studies should be performed in order to validate the findings of the suPAR-mediated detrimental effect on the glomerular filtration barrier, as data from several suPAR animal studies seemed inconsistent in their findings, possibly because of the various experimental settings (genetic background of animals, doses, duration of suPAR exposure and suPAR measurement; Alfano et al. 2015; Cathelin et al. 2014; Hahm et al. 2017; Spinale et al. 2015; Wei et al. 2011).

In addition to the causative role of suPAR in FSGS, suPAR appears to be an early predictive marker for the development of a variety of renal diseases. A prospective observational study in a large cohort of patients with cardiovascular disease demonstrated that elevated serum

suPAR levels strongly predict the decline of renal function independently from baseline glomerular filtration rate (GFR) and is associated with the faster progression of chronic kidney disease (CKD; Hayek et al. 2015). This role of suPAR in predicting future CKD development has been corroborated by two independent prospective studies. Guthoff et al. (2017) showed that a higher baseline suPAR is associated with an increased risk of new-onset microalbuminuria in subjects at risk for type II diabetes and reliably predicts the onset of microalbuminuria, again independent of the baseline GFR. Schulz et al. (2017) demonstrated that suPAR predicts CKD incidence and kidney-related hospitalizations in healthy subjects up to 19 years earlier than CKD onset. Further studies are required to elucidate the precise role of suPAR in the heterogeneous pathogenesis of human CKD/FSGS. These include (1) the contribution of the molecular nature of suPAR (splice variants and differential glycosylation and proteolytic cleavage) to the development of CKD or the manifestation/recurrence of FSGS and (2) its possible additive detrimental effect in conjunction with other circulating factor(s). The role of suPAR as a biomarker for the prediction of CKD development may be independent from its effect on the podocytes in health and disease.

Bone marrow

Most recently, we identified immature myeloid cells within the bone marrow as the source of elevated suPAR in protein-uric kidney disease such as FSGS (Hahm et al. 2017). Given the possible central role of the bone marrow as the source of suPAR, bone marrow transplantation (BMT) from normal mice to proteinuric mice substantially reduces suPAR levels and subsequently improves kidney function. Transfer of bone-marrow-derived immature myeloid cells from proteinuric mice induces proteinuria and increases plasma suPAR levels in healthy mice. This study has expanded the role of bone marrow from being merely a place for hematopoietic cell production to its also being a key extrarenal regulator of the function of the glomerular filtration barrier by expanding suPAR-generating cells.

The contribution of bone marrow cells (or hematopoietic cells) to kidney function was revealed by two initial studies of animal models (Nishimura et al. 1994; Sellier-Leclerc et al. 2007). An early report of Nishimura et al. (1994) using an FGS/Nga mouse line in an animal model of spontaneously developing FSGS demonstrated that BMT from normal mice to FSGS mice induced the remission of proteinuria. Furthermore, healthy mice develop FSGS following the transfer of bone marrow cells or purified hematopoietic stem cells (HSCs) from FSGS mice. Sellier-Leclerc et al. (2007) introduced the technology of humanized mice and showed that the transfer of CD34⁺ hematopoietic stem progenitor cells (HSPC) from individuals with glomerular diseases into healthy mice can induce albuminuria, although the authors offered no mechanism for this result. Thus, our group engineered a modified FSGS humanized mouse model and further revealed that CD34⁺ cells derived from patients with recurrent FSGS but not from healthy individuals, are critical for the development of a suPAR-driven glomerulopathy and proteinuria, by triggering an expansion of mouse suPAR-producing cells in the bone marrow. This study suggests that hematopoietic dysfunction is one of the culprits for certain forms of CKD that are associated with high suPAR levels (Hahm et al. 2017) and implies that BMT or hematopoietic stem cell transplantation (HSCT)

represents a potential therapeutic option for the treatment of suPAR-associated kidney diseases, especially recurrent FSGS.

Therapeutic potential of BMT for recurrent FSGS

In the clinic, the management of recurrent FSGS is controversial and difficult. The mainstay of treatment for recurrent FSGS is PP (or PE) or immunoadsorption. In combination with PE or alone, high-dose steroids, intravenous cyclosporine, and rituximab have been used. Although a renal transplant is the best treatment option for patients with ESRD, renal transplantation in patients with underlying FSGS as a native disease can be challenging, especially when faced with the possibility of recurrent disease and the high likelihood of allograft failure in such an instance. Acute renal dysfunction after transplantation can be caused not only by immunological rejection either at the graft (graft rejection) and/or at the host (graft-versus-host disease, GVHD) end but also by the recurrence of the original disease. Prospective studies suggest that the incidence of nephrotic syndrome attributable to GVHD is independently associated with CKD (Saddadi et al. 2017; Weiss et al. 2006). Moreover, the long-term administration of immunosuppressive agents for the prevention of GVHD and graft rejection results in a number of toxicities, including renal dysfunction, opportunistic infections and malignancies. Thus, many attempts have been made to induce immune tolerance for solid-organ transplants. One approach to tolerance induction is mixed hematopoietic cell chimerism, a coexistence of donor and recipient hematopoietic cells. Chimerism has been shown to prevent graft rejection and to induce graft survival in rodent models (Huang et al. 2000; Ildstad and Sachs 1984) and in large animal models (Kawai et al. 1995; Kimikawa et al. 1997).

Is HSCT safe and feasible for preventing the post-transplantation recurrence of renal disease leading to CKD? HSCT is also a challenging option that can induce CKD. Two systemic analyses by Ellis et al. (2008) and Cohen et al. (2010) revealed that between 15% and 17% of patients undergoing HSCT develop CKD. A single-center retrospective study (2001 ~ 2010) showed that CKD occurred in about 20% (47 out of 230) of patients who had undergone allogeneic HSCT for hematological disease (Sakellari et al. 2013).

Patients with pre-existing CKD are generally excluded from HSCT because of the treatment-related morbidity and mortality. However, as CKD is a common complication of hematological malignancies or abnormalities such as myeloma or sickle cell disease, much of the evidence of co-existent CKD in HSCT comes from patients having undergone HSCT transplant for multiple myeloma. Successful HSCT was initially reported in one patient suffering from ESRD with multiple myeloma (Spitzer et al. 1999) at Massachusetts General Hospital (MGH). Given the patient's intolerance of dialysis and limited life expectancy because of the underlying multiple myeloma, consideration was given to a combined bone marrow and renal transplant after the conditioning of the patient with cyclophosphamide, antithymocyte globulin and thymic irradiation. No rejection episodes occurred and renal function remained normal. Buhler et al. reported two cases of ESRD caused by multiple myeloma having undergone simultaneous HSCT and kidney transplantation from human leukocyte antigen (HLA)-identical siblings. No rejection episodes occurred after the transplants. Both patients continued to have normal kidney function and sustained anti-

tumor responses, despite having received no immunosuppression for nearly 4 and 2 years, respectively (Buhler et al. 2002).

Further studies have broadened this application to patients without malignancies. Scandling et al. (2008) at Stanford University reported a case of a patient, who had idiopathic ESRD, who underwent a combined kidney and hematopoietic cell transplant from an HLA-matched donor and who had normal kidney function and achieved complete withdrawal of immunosuppressive drugs after the transplant. A study by Kawai et al. (2008) analyzed outcomes in HLA-mismatched patients with ESRD attributable to non-malignancy in a tolerance protocol of combined kidney and non-manipulated BMT. Irreversible humoral rejection occurred in one patient but four out of five patients retained the graft and maintained stable renal function with a complete withdrawal of immunosuppressive therapy. Another trial of combined HLA-mismatched hematopoietic and kidney transplant was reported by investigators at Northwestern University (Leventhal et al. 2012). In their trial, five out of eight subjects experienced durable chimerism, demonstrated immunocompetence and donor-specific tolerance by in vitro proliferative assays and were successfully weaned off all immunosuppression 1 year after transplant. Further, in a study by Scandling et al. (2015), 22 HLA-matched patients enrolled into the tolerance protocol at Stanford University over a period of 14 years were analyzed. Persistent chimerism for at least 6 months was associated with complete withdrawal of immunosuppressive drugs in 16 of 22 matched patients without rejection episodes or kidney disease recurrence with up to 5 years of follow-up. None of the patients enrolled had kidney graft loss or GVHD with up to 14 years of observation (Scandling et al. 2015). Strober (2016) reviewed a total of 41 HLA-matched and mismatched patients who were treated in three medical centers (MGH, Stanford University and Northwestern University) and who could be completely withdrawn from immunosuppressive drugs after combined kidney and HSCT transplantation and concluded that HSCT is a feasible approach leading to the complete withdrawal of immunosuppressive drugs from kidney transplant patients with follow-up periods of up to 10 years (median: 20 to 62 months). A prospective single-center study (Vanikar et al. 2013) also reported that kidney transplantation by using HSCT in thymus, bone marrow and the portal and peripheral circulation safely and effectively prevents recurrent FSGS in patients with biopsy-proven primary FSGS. In summary, successful combined bone marrow and kidney transplantation has been reported and shown promising outcomes in patients with ESRD attributable to myeloma or with primary or secondary kidney diseases.

Concluding remarks

Plasmapheresis, the most commonly used treatment for recurrent FSGS, has been shown to provide partial or complete remission in 60–70% of patients. High-dose steroids, intravenous cyclosporine and rituximab have also been shown to prevent the recurrence of FSGS. However, the management of recurrent FSGS remains difficult and frustrating. The post-transplant complications are also challenging. Patients with kidney transplants need to use immunosuppressive drugs for the rest of their lives to prevent rejection; such drugs typically cause a number of serious side effects such as renal dysfunction, opportunistic infections and malignancies.

Given recent evidence that the predominant source of the podocytopathic suPAR that is possibly responsible for the recurrence of FSGS is in the bone marrow, which is “extrarenal”, it is tempting to consider BMT as a potential therapeutic option for the prevention of FSGS. Interestingly, newer clinical trials have provided valuable insights indicating that combined kidney and hematopoietic cell transplantation is a feasible and safe therapeutic option for devastating renal diseases such as recurrent FSGS. The possible mechanisms by which combined transplants resolve renal graft function include (1) the prevention of recurrence by the limitation of host hematopoietic cells responsible for the recurrence of the original disease, (2) the hindrance of the immune rejection (GVHD and graft rejection) by inducing tolerance, (3) the prevention of chronic renal injury attributable to long-term immunosuppression.

Having defined the extrarenal origin of suPAR and its pathological role in the kidney filter function, together with PP/immunoabsorption that eliminates circulating factors including suPAR, we consider that the concomitant application of BMT or HSCT might be a successful and suitable way of treating ESRD, including recurrent FSGS.

Whereas combined bone marrow and kidney transplants have shown promising outcomes in patients with ESRD attributable to myeloma, their utility in other primary or secondary kidney diseases is currently not considered as representing a suitable standard of care because of uncontrolled or small sample sizes or short-term follow-up studies. Future research focusing on suPAR measurements after transplant will be of great interest for exploring the pathological mechanisms of recurrent FSGS and even other idiopathic renal diseases.

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