

Cell-Based Therapies as an Adjunct to Revascularization in Experimental Atherosclerotic Reno Vascular Disease

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Atherosclerotic renovascular disease (ARVD) is a reversible cause of secondary hypertension that accounts for almost 7% of individuals older than 65 years old, and is implicated in over a third of all cases of end-stage renal disease (ESRD) in the United States [1]. Importantly, ARVD is associated with increased risk of myocardial infarction, congestive heart failure, stroke, peripheral artery disease, and mortality [2].

Renal revascularization by percutaneous transluminal renal angioplasty (PTRA) is commonly performed in ARVD patients. However, twenty-five years after the first successful PTRA [3], its role remains uncertain. While small clinical studies have reported significant improvement in blood pressure and renal function among PTRA-treated patients [4,5], large randomized clinical trials failed to determine an incremental value of PTRA, on a top of medical therapy, for the treatment of ARVD [6,7]. In agreement, we have previously shown in a swine model of ARVD that PTRA normalizes blood pressure levels, but fails to improve tubulointerstitial injury, microvascular rarefaction, and renal function in the stenotic kidney [8].

One of the potential explanations of the unfavorable renal outcomes after PTRA could be the activation of multiple deleterious pathways in the post-stenotic kidney tissue. It is well known that activation of renin-angiotensin system, oxidative stress, apoptosis and fibrosis in ARVD leads to tissue injury and might compromise response to renal revascularization [9]. Moreover, damage of the renal microcirculation is an important determinant of tubulointerstitial and glomerular fibrosis beyond the stenotic lesion [10]. Accordingly, intra-renal administration of the angiogenic factor vascular endothelial growth factor (VEGF) has been shown to attenuate fibrosis and microvascular damage, improving renal function after PTRA in chronic experimental ARVD [11]. Renal inflammation has also been identified as a key mediator of tissue injury and progressive renal dysfunction in ARVD [12]. We have recently shown that the post-stenotic human kidney releases numerous inflammatory mediators leading to a progressive compromise of renal function [13]. Taken together, these observations emphasize the need for more effective strategies in addition to revascularization to improve renal outcomes in ARVD.

Therapeutic utilization of allogeneic and autologous stem cells is becoming an attractive alternative to conventional treatments for several diseases. Circulating endothelial progenitor cells (EPC), mobilized and recruited after renal ischemia, play a key role in repairing ischemic tissues in experimental models of renal injury [14]. Their mobilization from bone marrow and recruitment to the injured kidney is regulated by the release of homing factors such as stromal cell-derived factor (SDF)-1 and stem cell factor (SCF). Our group has demonstrated that delivery of EPC in the stenotic ARVD kidney improved renal hemodynamic and function and decreased the release of endogenous injury signals from the stenotic kidney [15,16]. In line with these observations, we have shown in swine ARVD that intra-renal delivery of autologous hematopoietic EPC during PTRA improved renal hemodynamics and function in the post-stenotic kidney [17]. Moreover, oxygen-dependent tubular function and microvascular architecture were normalized and

fibrosis and inflammation reduced in PTRA+EPC-treated animals, underscoring a novel regenerative potential for EPC in experimental ARVD. However, a significant disadvantage of EPC therapy is the fact that in order to generate autologous EPC, mononuclear cells must be isolated from peripheral blood, and expanded in vitro, which requires collection of large amounts of peripheral blood from each individual.

Over the last decade, mesenchymal stem cells (MSC) have emerged as an alternative therapy for a range of renal injuries. These cells possess extensive proliferation potential, unique anti-inflammatory properties, and can be isolated from a variety of tissues, such as adipose tissue and bone marrow [18]. Experimental studies have revealed the ability of MSC to stimulate renal parenchymal regeneration and attenuate kidney injury secondary to ischemia/reperfusion injury [19-21]. Consistent with these results, we have demonstrated in swine ARVD that intra-renal administration of adipose-tissue derived MSC improved renal function and structure after revascularization and reduced oxidative stress, apoptosis, fibrosis, inflammation, and microvascular remodeling in the stenotic kidney [22]. Importantly, histological analysis showed no evidence of cellular rejection, micro-infarcts, or tumors in PTRA+MSC-treated pigs. Therefore, our findings uncovered a unique renoprotective effect of MSC to restore renal cellular integrity and repair mechanisms in experimental ARVD.

In summary, ARVD is a prevalent and progressive disease for which the optimal therapeutic strategy remains to be elucidated. While PTRA may reduce blood pressure, improvement of renal function is not commonly achieved, warranting adjunctive therapies. Cell-based therapies with EPC or MSC appear to be safe and effective approaches to improve renal outcomes in experimental ARVD. Additional studies are needed to evaluate the clinical therapeutic benefit of these strategies.

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