Intra-renal Transplantation of Bioactive Renal Cells Preserves Renal Functions and Extends Survival in the ZSF1 model of Progressive Diabetic Nephropathy

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ABSTRACT: There are >200,000 diabetic patients in the US with End-Stage Renal Disease. Hemoglobin A1c and glomerular filtration rate are inversely correlated with patient survival and quality of life. Despite the increasing prevalence of diabetic nephropathy, few treatment options exist to improve renal function and survival. Intra-renal injection of bioactive renal cells (BRCs) into ZSF1 rats has been shown to stabilize kidney mass, stabilize filtration function, and extend survival following in vivo renal delivery. In 5/6 nephrectomy models of progressive diabetic nephropathy, BRCs preserved normal renal functions and extended survival. Improved physiological parameters observed in the ZSF1 model included improved filtration and tubular function, improved whole organ function, and reduced circulating PAI-1.

RESULTS

1. In the present study therapeutically-relevant bioactive renal cells improve a myriad of renal functions affected by treatment significantly predicted ZSF1 survival beyond the one year timeline for follow up. The characteristic hypertension in the ZSF1 model was attenuated at 50 weeks of age by BRC treatment. These data were further supported by histologically significant evaluation of physiological parameters of blood pressure, including the pressure hormones, ACTH, and renin and renin-angiotensin-aldosterone system consistent with previous results. Regulation of the BRCs in the ZSF1 model resulted in significant reduction of circulating plasminogen activator inhibitor (PAI-1), a master regulator of tissue fibrosis.

METHODS: ZSF1 rats were purchased from the vendor Charles River Laboratories and delivered to a Central Animal Research Facility in Winston-Salem, NC. Animals were housed and monitored for 8 weeks prior to treatment. All procedures were conducted in accordance with NIH and IACUC guidelines. A total of 120 rats were evaluated for the analysis presented. Rats were either injected with 3 million bioactive renal cells (BRCs) (implantation into the right and left kidney parenchyma, accessed via the cranial and caudal poles of each kidney, using a 23 gauge needle. A cell dose of 3.0 million cells in 100 µl sterile PBS was administered bilaterally to each kidney pole for a total dose of 6.0 million cells/~2.5 g kidney. The suspended cells were loaded into a 1-ml syringe fitted with a ½-inch 23-gauge needle and delivered directly to the kidney through a small incision in the peritoneum) or remained untreated (control). Whole kidney function was assessed using urine output, composite renal function, and survival. Whole kidney function was assessed using in-life assessment for controlling hyperglycemia (switch from Rosiglitazone to Metformin). Biopsy tissue was isolated from the primary culture established from adult female ZSF-1 (6-8 week old) kidneys using established protocols. Tissue was maintained in accordance with NIH and IACUC guidelines, and tissue samples were collected at 18 weeks post-treatment (18 weeks of age) or following standard of care measures for controlling hyperglycemia (switch from Rosiglitazone to Metformin). Data compiled from all animals (Obese and Obese Tx) that died prior to the end of study days (Day 315).

REFERENCES:

1. Kelley et al., 2016 J.P. Renal Physiol. 211 (5)