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Novel delivery of cell therapy in normothermic machine perfusion to reduce ischaemia reperfusion injury in kidney transplantation

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Introduction: Kidney transplant is the gold-standard treatment for the rising number of patients with renal failure. However, the shortage in donor organs has led to increased reliance on marginal kidneys. Normothermic machine perfusion (NMP) prior to transplantation provides a platform for direct delivery of cellular therapeutics to revive, optimise and restore function prior to transplantation. Multipotent Adult Progenitor Cells (MAPCs) are a type of adult, bone-marrow derived, mesenchymal stem cell that possess potent immunomodulatory properties in vitro which could prove beneficial in minimising ischaemia reperfusion injury (IRI) during NMP.

Methods: Pairs of human kidneys (deemed unsuitable for transplant) from the same donor were simultaneously perfused for 7 hours (n=10). Following 1 hour of perfusion $50x10^6$ MAPCs were delivered as a bolus into the kidney's arterial cannula. Physiological recordings were taken at 30 minute intervals. Serial samples of perfusate, urine and tissue biopsies were taken for cytokine profiling and biomarker analysis.

Results: MAPC treated kidneys demonstrated improved urine output, $p<0.01$, decreased expression of tubular injury biomarker NGAL $p<0.01$, improved microvascular perfusion on contrast enhanced ultrasound (cortex $p<0.05$, medulla $p<0.01$), downregulation of endothelial activator IL-1β ($p<0.05$) and upregulation of anti-inflammatory, pro-tolerogenic molecules IL-10 ($p<0.05$) & Indolamine-2, 3-dioxygenase ($p<0.05$). Immunofluorescence confocal microscopy co-localisation studies revealed fluorescent-labelled MAPCs were resident within the kidney parenchyma via diapedesis (figure 1). A mouse model of intraperitoneal chemotaxis demonstrated decreased neutrophil recruitment when stimulated with MAPC perfusate ($p<0.01$). An endothelial cell model demonstrated the MAPC perfusate protected endothelial integrity and decreased vascular permeability by increasing S1PR1 gene ($p<0.05$) and protein expression ($p<0.0001$) in HMEC-1 cells.

Conclusion: Kidneys treated with MAPCs during NMP demonstrate improvement in clinically relevant parameters and biomarkers associated with IRI. The anti-inflammatory MAPC perfusate secretome reduced neutrophil chemotaxis and protected the endothelium. This novel method of cell therapy delivery provides an exciting opportunity to recondition organs prior to clinical transplantation.

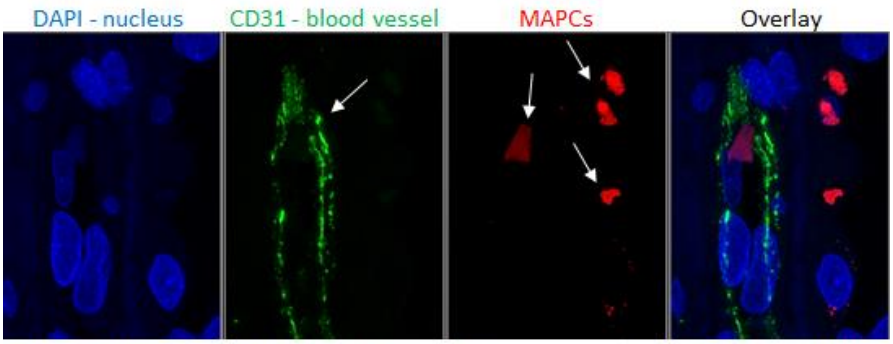

Figure 1: MAPC tracking in kidney NMP. Immunofluorescent confocal microscopy of kidney sections after 6 hours of MAPC therapy. 63x magnification of blood vessel from wedge biopsy.