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Improving Renal Extracellular Matrix Endothelialization with MSC-GEC Co-culture

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Description

Addressing the challenges posed by the limited regenerative capacity of kidneys and the scarcity of kidney donors, dialysis remains the primary treatment option for many patients with End-Stage Renal Disease (ESRD). However, dialysis is considered a temporary solution due to its inefficiency in clearing large and protein-bound uremic solutes, which can exacerbate disease progression over time. The imbalance between kidney donors and recipients presents an ongoing challenge, necessitating urgent exploration of alternative approaches to bridge this clinical gap. Acute Kidney Injury (AKI), characterized by a sudden rise in serum creatinine levels and reduced urine output, often evolves into chronic kidney disease. Recent advancements in tissue engineering and regenerative medicine offer various cell-based strategies to address renal failure. One promising approach involves regenerating the kidney Extracellular Matrix (ECM) scaffold through decellularization followed by recellularization, aiming to create a functional tissue substitute. Despite increasing interest in using decellularized whole kidneys as 3-Dimensional (3D) scaffolds to create ex-*vivo* renal tissue, numerous questions remain unanswered.

Stem cells

The concept of extracting a kidney for decellularization and subsequent recellularization with restored function presents significant challenges. Recellularization of the entire kidney in conjunction with stem cells represents a potential strategy for regenerative medicine. In the context of renal organ recellularization, the culture Flow Rate (FR) plays a critical role in the vascular system, with a high FR potentially leading to increased expression of cell death markers in endothelial cells. Hypertension, a prevalent disease characterized by sustained high blood pressure, is a significant contributor to kidney failure. The damaging effects of hypertension on kidney vasculature can lead to chronic kidney disease, with symptoms such as increased protein in the urine due to glomerular damage. Therefore, we hypothesized that an uncontrolled flow rate might adversely affect glomerular morphology and endothelialization. Previous studies have reported recellularization of renal organs across a wide range of flow rates, highlighting the importance of FR in the vascular system and its potential to induce inflammatory responses and edema. In this study, we aimed to optimize the flow rate in recellularized renal extracellular matrix scaffolds with renal glomerular endothelial cells for successful growth and function. An experimental approach involving the use of a monoculture of renal Glomerular Endothelial Cells (rGECs) was employed for the recellularization of a renal Extracellular Matrix (ECM) scaffold, which was subsequently subjected to co-culture with renal Bone Marrow-derived Mesenchymal Stem Cells (rBMSCs).

Renal vessels

The rBMSCs were selected due to their ability to enhance the survival of rGECs and promote essential cellular processes including attachment, migration and the secretion of pro-angiogenic factors such as VEGF, Ang2, Tie2, VEGFR2, among others. This cell therapy concept aimed at renal vessel recovery *in vitro* demonstrated that local Mesenchymal Stem Cells (MSCs) possess the capacity to differentiate into endothelial cells and contribute to renal repair primarily through paracrine actions, notably by producing Vascular Endothelial Growth Factor (VEGF) to prevent microvascular deterioration. Previous studies have also indicated that bone marrow-derived MSCs can differentiate into endothelial cells and protect against ischemic renal injury *via* mechanisms independent of differentiation upon systemic administration. Local MSCs have been identified as valuable carriers in cell therapy for promoting tissue regeneration following Acute Renal Failure (ARF). The objective of our current investigation was to develop an artificial renal scaffold using a decellularization system while preserving the structural integrity of the vascular ECM. Furthermore, the formation and adhesion of blood vessels within the renal scaffold were confirmed using a bioreactor, with particular interest in examining vascular endothelial cell adherence. Our hypothesis posited that the combined application of rGECs and rBMSCs would enhance scaffold attachment and facilitate regeneration towards native kidney vessel cells through immunomodulatory processes.