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The use of stem cells as a therapeutic modality for amelioration of chronic renal damage after warm or cold ischaemic insults

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Several epidemiological studies have shown that AKI is a risk factor for progression to CKD. IRI is one of the main causes of AKI, and for that reason, murine models of AKI are mostly based on renal ischaemia, although in most cases the observation time of these studies is too short to draw reliable conclusions regarding the long-term outcomes. This study provides a description of the long-term renal outcomes of murine models of warm ischaemia and addresses the current discrepancies in scientific literature concerning the role of the renal mass at the time of ischaemic injury. Furthermore, the transcutaneous evaluation of kidney function was implemented measuring FITC-S clearance.In the context of warm ischaemia models, unilateral ischaemia without contralateral nephrectomy at the time of injury led to long-term kidney function deterioration, once the non-ischaemic kidney was removed. Additionally, histopathological analysis revealed cyst formation, increased number of ED1+ macrophages and a higher extent of interstitial fibrosis compared to the animals nephrectomised right after ischaemic injury. Thus, this model makes a good candidate for interventional studies. Since AKI patients have to rely in supportive care and renal replacement therapy, new therapeutic modalities are greatly needed. Thus, MSC as well as MSC conditioned media therapies have become an interesting choice because of their many attributed properties. Therefore, in this study the treatment with hASC was implemented in the aforementioned warm ischaemia model, with a single injection 14 days after injury. The main finding was a strong reduction of ED1+ macrophages in the post-ischaemic kidneys of the cell treated animals vs. vehicle-treated. This might be explained by the notion that in a pro-inflammatory milieu, hASC adopt an immunosuppressive phenotype that might lead to PGE2 production by hASC, causing monocyte polarization to M2 macrophages. Cold ischaemia and minor MHC disparity were implemented in order to increase the severity of the model and achieve strong clinical and morphological end-points. This was indeed attained using a Fischer-Lewis kidney transplantation model with 8 hours of cold ischaemia. Thereafter, the treatment with ABCB5+ cells and its derived CM was implemented, one day before and seventeen days after KTx. Neither of the treatments was able to significantly ameliorate any kidney function parameter, although a trend toward worsened kidney function was observed in the cell-treated group. Likewise, the number of ED1+ macrophages and CD3+ T cells in the kidney grafts was not significantly reduced by either treatment. This lack of inhibition might be explained by the cell pre-treatment, as it has been reported that when no inflammation is present MSC can switch to a pro-inflammatory phenotype. As for the Banff classification scores, this model leads to lesions mostly associated mostly to T-cell mediated rejection. In all four criteria no great difference between the control group and CM-treated group were observed, besides a trend toward improved vasculitis and interstitial fibrosis in the CM-treated group. This might be attributed to the angiogenic and anti-fibrotic potential of MSC secretome components.