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EDITORIAL

Combining cell-based therapy and normothermic machine perfusion for kidney graft conditioning has gone one step further

Kidney transplantation (KTx) from donors after circulatory death (DCD) and extended criteria donors is being increasingly performed to overcome organ shortage. However, these transplants are more vulnerable to ischemia/reperfusion injury (IRI), which has prompted intensive research for graft-conditioning strategies. In addition to their immunomodulatory properties, mesenchymal stem/stromal cells (MSCs) proved efficient in the attenuation of renal IRI in pre-clinical models. Still, the optimal conditions of MSC use in clinical settings of KTx remain elusive.

Machine perfusion (MP) offers a great window of opportunity for organ conditioning prior to KTx, allowing for the evaluation/conditioning of the graft depending on its state and need. Among the various potential additives to preservation solutions during normothermic MP (NMP) (oxygen carrier, antioxidants, etc), cellular therapy has been evaluated.¹ Two recent studies support (1) a sufficient MSC survival and function rate in NMP conditions² and (2) the technical feasibility of human MSC administration during NMP of porcine kidneys, with an eventual accumulation in glomerular capillaries.³ Perfusion of kidneys grafts from DCD with human MSC in an ex vivo perfusion device for 24 hours (exsanguinous metabolic support) has been shown to enhance renal regeneration.⁴ Therefore, combining both NMP and cell therapy may lead to innovative promising perspectives in graft conditioning.

In this issue of the *American Journal of Transplantation*, Thompson et al⁵ provide additional preclinical information regarding the use of multipotent adult progenitor cells (MAPCs) for ex vivo kidney conditioning during NMP. They show that such a combined strategy is feasible and safe since no serious event linked to cell-based conditioning was reported. The study draws on significant strengths, including (1) the use of both human kidneys and MAPCs, thereby avoiding the interspecies confounding factors; (2) the paired study design in which each kidney from a single donor was assigned to either control or cell-based therapy, thereby limiting bias of interindividual heterogeneity; and (3) the choice of a clinically relevant cell infusion timing (ie, 1 hour after the perfusion initiation), thereby avoiding the potentially deleterious effects of an early reperfusion storm.

The main limitation of the study clearly relies on the short follow-up, which only includes 7 hours of perfusion. This hampers the interpretation of middle-term outcomes, such as kidney function parameters

and biopsy-proven acute rejection. Indeed, Thompson et al suggest a decreased renal IRI following MAPC-based NMP only based on improved microvascular perfusion and decreased urinary excretion of the biomarker NGAL, compared to controls.⁵ Additionally, a thorough evaluation of the impact of NMP perfusion fluid on the viability and behavior of MAPCs is lacking regarding previous results.² There is no clear confirmation in the work of Thompson et al that MAPCs are indeed still alive during the experiments. The authors report a ≈20% MAPC viability after 7 hours of NMP which may, however, be under- or over-estimated due to the filter placed for cell-counting purposes. Given the innovative design of the study, some iterative sampling during perfusion would have been worthwhile because these data are crucial before clinical implementation. Additionally, one can expect that longer durations of MP, similar to those used in clinical settings, would negatively impact cell survival. The potential subsequent systemic circulation of MAPCs in the recipient after transplantation of the conditioned graft raises the question of whether cell therapy directly applied during conditioning does or does not induce a risk of over-immunosuppression, while at the same time reproducing the beneficial effects previously reported.

Finally, cell-based strategies development also requires a focus on the cellular product itself. MAPCs are adult, bone marrow-derived stromal cells displaying properties similar to MSCs with regard to anti-inflammatory and immunomodulation properties. However, MAPCs and MSCs are obtained using distinct procedures and culture conditions, which may result in distinct phenotyping population including surface markers and hemocompatibility, which has not been addressed in Thompson's study.⁶ Thus, this study cannot be completely compared with other preclinical studies of reference showing encouraging results with MSCs.

In conclusion, the work of Thompson et al opens up new avenues and leads to high expectations regarding the implementation of cell-based therapy in graft conditioning during MP. We are looking forward to studies including the factual transplantation of cell-conditioned kidneys in preclinical models. However, gaps in knowledge include the need for a better in vivo understanding of the cellular and molecular mechanisms underlying the tissue-repair properties of MAPC/MSC in the particular MP setting. Cell behavior and fate during conditioning need to be better addressed. The benefit of an additional MAPC/MSC infusion after KTx to


eventually sustain the nephroprotection should also be evaluated. In addition, accumulating data suggest that MSC transitory presence and beneficial effect could be mimicked by cell secretome.⁷ Indeed, one considerable perspective relies on the characterization and use of cell-free alternatives such as cell-derived exosomes. This approach would facilitate some safety issues relative to the injection while mimicking beneficial effects.

KEYWORDS

cellular transplantation (non-islet), editorial/personal viewpoint, ischemia reperfusion injury (IRI), kidney transplantation/nephrology, organ perfusion and preservation, regenerative medicine, stem cells

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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