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Therapeutic potential of human kidney-derived stem/progenitor cells in a cisplatin-induced renal injury model

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Kidney diseases still face the lack of effective therapies to prevent progressive loss of renal function after initial damage. In addition, the monitoring of disease progression or recovery after therapeutic interventions has been limited by the constraints of the traditional methods used to evaluate renal function. Altogether, these facts lead to annual increases in the incidence of end-stage renal disease, for which the only treatment options are dialysis or renal transplantation. Therefore, appropriate diagnostic tools and new therapeutic approaches are urgently required.

In this study we evaluated the therapeutic potential of human kidney-derived cells from adult and juvenile renal tissues in a cisplatin renal injury model. Cisplatin is a widely use chemotherapeutic drug with deleterious nephrotoxic effects. The animal model was developed in immunodeficient rats in order to minimize possible rejection of human cells. To induce renal injury cisplatin was administered intraperitoneally at the dose of 7 mg/kg body weight. The progression of damage was studied sequentially during short- and long-term periods (14 and 60 days, respectively). The transcutaneous assessment of renal function was implemented as the main diagnostic method, but blood and urine parameters were also analysed for the characterization of the model. Histological samples were collected at the end of the experiments. The results indicate a successful establishment of renal injury after cisplatin treatment, characterized by a decline on kidney function, unbalanced blood and urine parameters as well as morphological alterations in renal tissue. Cisplatin-induced kidney nephrotoxicity showed a peak of damage by day 7. In addition, our experiments demonstrated that renal impairment and kidney tissue sequelae remain up to 60 days following cisplatin administration.

The developed animal model was then used to assess the therapeutic potential of human kidney-derived cells. Two different sets of cells were evaluated: 1) Human adult kidney epithelial cells induced to stably overexpress SIX2 and OSR1&SIX2 genes were evaluated along with control cells carrying an empty vector; 2) $CD133^+$ and $CD133^-$ cells isolated from human juvenile kidney. Our results demonstrate that all the cell types assessed display a certain therapeutic potential. However, OSR1&SIX2 and $CD133^+$ cells appeared to be more effective in this animal model. The therapeutic benefit was observed both at functional and morphological level. The cell treatments led to an amelioration of cisplatin nephrotoxic effects, preventing the loss of renal function as well as reducing the impact of cisplatin on blood and urine parameters, such as creatinine and urea. Renal tissue was also more preserved in animals undergoing cell treatment, further supporting the in vivo observations.

Attempts to localize the administered cells were made by using immunofluorescence techniques. However, no conclusive findings can be drawn. The presence of human cells in the renal tissue was generally a rare event. We found evidence that a few cells pass through the lungs, suggesting that many of them could died there without reaching the kidneys. Despite this, the beneficial effects of these cells were clear and significant. Therefore, these observations suggest a mode of action based on paracrine effects and not due to engraftment and proliferation of the administered cells.

In conclusion, this work demonstrated that the transcutaneous assessment is suitable to monitor the progression and recovery from cisplatin-induced nephrotoxicity and that human kidney-derived stem/progenitor cells are a viable option for regenerative cell therapies. Follow-up studies are necessary to investigate how to enhance the therapeutic potential of these cells, clarify their mode of action, optimize the therapeutic regimen and investigate their application in different renal conditions.