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Therapeutic potential of human ABCB5+ cells and different conditioned media in a cisplatin-induced nephrotoxicity model

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Kidney diseases are a global public health problem that lacks of effective therapies to prevent progressive loss of renal function after initial damage. Every year, we witness a continuous increase in the incidence of ESRD, for which the only available treatments are dialysis or renal transplantation. Being these two therapeutic options not only invasive for the patients, but also highly expensive for the public health system, new treatments are urgently required. In this scenario, stem cell therapy represents a promising approach for the treatment of renal injuries. Several studies have been conducted in this direction, but still no consensus has been achieved in terms of cell source, dose, timing and administration route to be used. In addition, the modes of action with which stem cells perform their therapeutic effects remain unclear and need further explanations.
In this study, we established a well-defined animal model of cisplatin-induced kidney injury that was then used to assess the therapeutic potential of ABCB5+ cells and derived conditioned media.
For the development of the animal model, we induced renal damage in immunocompetent SD rats by using a single ip injection of cisplatin, a well-known nephrotoxic drug, at the dose of 7 mg/kg BW. The onset and progression of the disease has been characterized on the basis of plasma, urine and metabolic parameters, renal function transcutaneously measured, histological evaluation and both mRNA and miRNA expression profiling. The analyses performed indicated the successful establishment of a stable cisplatin-induced nephrotoxic model that was then used to assess the therapeutic potential of ABCB5+ cells and derived conditioned media. The following treatments have been tested: 1) ABCB5+ cells both iv and ip administrated; 2) ABCB5+ cells derived conditioned media iv administrated (CM, CM+, coCM+).
The results showed that when animals were treated with ABCB5+ cells, we have not been able to see any amelioration in the plasma and urine parameters, renal function and histology and we did not observe any differences between the two applied administration routes. However, these animals did undergo genomic changes, which were even different in the two groups. Indeed, based on the gene expression analysis performed in renal tissue, it seems that the ipABCB5+ cell treatment triggered new cell formation and promoted a higher reduction of inflammation compared to the ivABCB5+ cell one.
In contrast, when three different conditioned media were administrated to the animals, we were able to see changes at the functional level. Indeed, markers of renal function, such as plasma creatinine and urea and urine albumin, were ameliorated especially after CM and CM+ treatments, while animals which received coCM+ did not show any deviation from the control animals. A similar trend was observed when the transcutaneous assessment of renal function was performed. Additionally, CM and CM+ treated animals did not lose appetite and therefore they did not show the typical loss of weight observed in the other experimental groups.
However, at the genomic level, coCM+ treated group exhibited better results in terms of reduction of inflammation and new cell formation, showing some similarity with the ipABCB5+ cell treated group. Also in the CM treated group a reduction of inflammation was reported, while CM+ treated animals did not show any relevant changes when compared to the cisplatin-induced nephrotoxicity model. Additionally, BP-GO analysis of downregulated miRNAs found in CM treated animals, showed their involvement mostly in metabolic processes, cell growth and response to wounding.
In conclusion, all together the results presented here demonstrate that CM displays the most pronounced therapeutic potential both at functional and genomic level in treating cisplatin-induced nephrotoxicity. For a possible translation to the clinical field, further studies to optimize the therapeutic regimen and to elucidate the involved modes of action are needed.