Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Long-term effects of different stem cells in genetic models of Cystic Kidney Disease

Autor: Daniela Nardozi
Institut / Klinik: Zentrum für Medizinische Forschung
Doktorvater: Prof. Dr. N. Gretz

Cystic kidney diseases are a global public problem, as the population of patients is increasing at a rate of approximately 7% per year. Unfortunately, up to now there is a lack of efficient therapies that can prevent the progressive loss of renal function. Drug treatment is of limited. The only therapeutic alternatives are dialysis or kidney transplantation. Nevertheless, the human and economic impact of the diseases to affected individuals and to medical community and society alike is enormous. Therefore new therapies are urgently needed. Stem cell application represents a promising therapeutic approach. MSC therapies have been used extensively, in the recent years, as a possible therapy for other kidney diseases with the aim of slowing down the course of the disease. However, many aspects remain unclear or are under debate like the finding of an appropriate source of MSCs, the understanding of their modes of action and, not least, the dose and timing of the administration.

Aim of this study was to evaluate the potential therapeutic effects of two different types of stem cells, and the derived conditioned media, in two animal models resembling human cystic kidney diseases. In order to achieve this goal, firstly we characterized, on a long-term basis, two different genetic animal models: the PKD/Mhm (Cy/+) and the PCK rats. Afterwards, we performed a 6 months trial, to test the long-term effects of human ASC and human ABCB5+ cells and ASC derived CM and ABCB5+ derived CoCM+. Animals were classified in four different groups, depending on the treatment received: (i) group that did not received treatment, (ii) ASC derived CM or ABCB5+ derive CoCM+ group, (iii) i.p. ASC or ABCB5+ group and (iv) i.v. ASC or ABCB5+ group. The progression of the disease and the effect of the treatments were determined on the basis of plasma and urine biochemistry, transcutaneous measurement of renal function, histology evaluation and gene expression profiling.

Our results found a different disease severity in the two models. PCK rats presented, since the beginning of the project, worse clinical manifestations compared to PKD/Mhm (Cy/+) probably due to the different genetic background.

ABCB5+ and ASC treatments led to an improvement in renal function reflected by GFR, plasma levels of creatinine, albuminuria and proteinuria, in PKD/Mhm (Cy/+) model. Histological evaluation of the kidney revealed a reduction of apoptosis and cell proliferation. Moreover, comparable genetic changes were reported after these treatments. Also the ABCB5+ derived CoCM+ treatment proved to ameliorate the biochemical parameters, while ASC derived CM treatment had a lesser pronounced outcome. Both after ABCB5+ derived CoCM+ or ASC derived CM administration the histological changes in apoptosis and proliferation reduction was observed. Ultimately, these animals undergo to genetic changes similar to the one observed after the cells treatment.

Concerning the PCK model. ABCB5+ and ABCB5+ derived CoCM+ treatments slightly ameliorated kidney function, plasma and urine parameter and likewise the levels of apoptotic and proliferative positive markers. Administration of ASC or ASC derived CM improved the renal function and decreased the apoptotic and proliferative positive cells but had only a mild effect on other parameter involved in the kidney function. Additionally, the gene expression profile did not highlight significant genetic changes after those treatments, while ABCB5+ and ABCB5+ derived CoCM+ administrations induced beneficial genetic changes.

In conclusion, our results demonstrate that ABCB5+ or ASC cells administration, either i.v. or i.p., and ABCB5+ derived CoCM+ might be a valid alternative therapy for cystic kidney diseases. However, before a possible application in the clinical field further studies need to be carried out in order to better define the mode of action and the side effects of these therapies.