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The immunomodulatory and pro-regenerative capacity of mesenchymal stromal cells and their therapeutic use for kidney disease

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In this study, we aimed to improve our knowledge on MSC therapy in acute kidney injury. Overall this work, being part of the International Research Training Group Renal Tool Box, addressed three different projects: 1. An inter-laboratory study on harmonising MSC culture and analysis procedures, 2. Evaluating whether human MSC therapeutic options can be fully understood in using xenogenic mouse models, given that the immune systems differ largely and MSCs function relies to a large extent on modulating immune responses and 3. Hypothesizing that adding MSC CM to a co-culture setting of PTEC and macrophages could have additive effects upon cisplatin injury.

In Part 1, we established standard tissue culture conditions for the expansion of adipose, bone marrow and umbilical cord MSCs among three independent centres across Europe to investigate the reproducibility of harmonised manufacturing procedures and its impact on their immunomodulatory capacity on PBMC proliferation. We show that harmonised protocols improve reproducibility across different centres emphasizing the need for worldwide standards to manufacture MSCs for clinical use. Further, tissue-specific differences in cell characteristics suggest selecting the optimal cell type for the intended clinical indication based on autologous or allogeneic use, source availability and functional characteristics. These results show the heterogeneous behaviour and regenerative properties of MSCs as a reflection of intrinsic tissue-origin while providing evidence that the use of standardized culture procedures can reduce, but not eliminate inter-lab and operator differences.

In Part 2, we demonstrated that MSCs/their secretome can modulate macrophage phenotypes even in xenogeneic setting. Despite the identical effect of MSC CM on macrophages from human and rat, the mediator contributing to it seemed to differ. We found out that in rat macrophage, TGF-β1 seemed to be the key mediator for pro-phagocytosis effect of MSC while in human PGE-2 plays a more important role.

In Part 3, we showed that CM was protective against cisplatin-induced injury of ciPTECs, which seems to be associated with its anti-oxidative properties. In contrast, CM could not rescue macrophages from cisplatin-induced cell death, but it rather promoted M2 polarization which is, however, compromised by cisplatin. Furthermore, the CM treatment in ciPTECs and macrophages co-culture abrogated ciPTEC death and dampened macrophage activation by attenuating macrophage cytokines and chemokines release. Surprisingly, this suppressing effect on macrophage secretion did not influence the CM effect on improving phagocytosis. Nonetheless, we did not observe the added benefit of macrophages in the CM renoprotective on ciPTECs. This might be caused by the fact that the CM already exerted very strong protective effect that it overruled the macrophage contribution in this system. Since our system did not allow direct phagocytosis of dead ciPTECs by macrophages, the macrophage role in CM-induced proximal tubule recovery could not be highlighted and should not be overlooked for clinical implementation of MSC secretome in the future.