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Mechanism of action of adipose mesenchymal stromal cells reducing cisplatin-induced proximal tubular epithelial cell injury

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Kidney disease is a serious health problem worldwide with an increasing prevalence. New research has made it possible to understand the pathophysiology of kidney disease better. However, there are still limited treatment options to stop or reverse the progression of the disease. Therefore, developing new strategies for treating kidney diseases is a critical area of research. In this context, cell-based therapy could be a promising strategy and is currently the focus of preclinical studies.
In our study, we asked ourselves whether mesenchymal stem cells could offer a novel cell-based therapy modality. Many questions remain open about choosing the source that best suits for your scientific question or using paracrine factors rather than cells. Moving on to the use of cell-free therapy raises other questions about the decision to use the whole secretome or just one component.
To find an answer to these questions, we structured this study in different levels, starting from the study of different cell types, passing later in the secretome and then moving on to a situation of injury.
First, we established harmonised tissue culture conditions for the expansion of adipose, bone marrow and umbilical cord MSC between three independent centres to study the reproducibility of these procedures and their impact on their biological characteristics and functionality both in vitro and in vivo. This part of the thesis highlights the importance of adopting harmonised protocols that reduce, but not eliminate, site-to-site variation while specific differences in donors remain evident. Despite the use of a common protocol, the different types of MSCs have shown individual properties, which may have benefits in specific therapeutic settings.
The aim of the secretome study was to test the in vitro efficacy of the different components for different aspects of tissue regeneration and at the same time understand how the different isolation methodologies can influence the results. Extracellular vesicles (EVs), regardless of the method of isolation, failed to replicate the results obtained by the secretome, in contrast, the protein fraction showed an effect very close to that of the secretome. We have shown that depending on the isolation method, contamination with protein residues can alter the results and misinform about the true efficiency of EVs. On the other hand, increased EV concentration in some applications increased effectiveness, indicating that purity and dose affect the final functionality.
At the end, we aimed to test the secretome in a situation of cellular damage in order to identify the beneficial effects and the molecular mechanisms involved to propose a therapeutic strategy. The administration of the conditioned medium protected the kidney cells by reducing cisplatin cytotoxicity, maintaining cell viability, stimulating cell migration, reducing apoptosis and apoptosis-related protein. We demonstrated that the conditioned medium reduced cell death by inhibiting the expression of mir-181a. We propose a so-called type II regulatory circuit by which A-MSC CM and cisplatin affect p53 expression/apoptosis and the counteracting miR-181a expression.