Modulating the distribution and fate of MSCs following therapeutic delivery may enhance their efficacy

Mesenchymal stem/stromal cells (MSCs) can be isolated from multiple adult tissues and have been shown to produce factors which can protect cells from diverse injurious stimuli, favourably modulate the immune response, and enhance tissue reparative and regenerative responses. Specific interest exists in the potential of allogeneic MSCs to combat infection (Bacterial and viral e.g. COVID-19) induced severe organ injury. Understand the movement, behaviour, and lifespan of MSCs administered into the human body may reveal strategies to further enhance MSC effectiveness in treating disease and injury.

How MSCs work: While initially thought that therapeutic MSCs would act by replacing damaged cells and tissues in the body, studies show MSC mainly act via the substances they release. MSCs appear influenced by their micro-environment - both inside the body and in the laboratory - and manipulation of these conditions may generate a more effective MSC. While MSCs can ‘home’ to sites of injury, they also exert therapeutic effects when remote from site of injury. Having the cells as close as possible to the injury site appears desirable as more of their produced factors would reach the intended target. Having the cells remain there as long as possible would also assist with enhancing the effect.

Therapeutic MSC distribution in the Body: MSCs are relatively large cells, approx. 2-8 times the size of a red blood cell and are not very flexible. As such when they are given intra-venously they become trapped in the small vessels of the lung during circulation. While potentially ideal for treatment of lung pathologies, this is less desirable for other organs when close contact is desired. MSCs leave lungs after a day, and small numbers are subsequently detected in kidney and liver. Strategies to avoid or overcome MSCs gathering in the lungs including injecting them into an artery, or directly at the injury site, or giving drugs which widen the blood vessels in the lungs. Of importance, modulating MSCs culture conditions can alter where they travel in the body after injection.

Current methods to determine MSCs Distribution: Insights on MSC distribution come largely from MSC imaging/detection studies of MSCs containing a tracking dye or label in animal models. Magnetic resonance imaging (MRI) or computed tomography (CT) are used to detect MSCs in the body. MSCs can be be detected post-mortem by removing the tissues and then finding the MSC dye or label, or looking for their genetic material. Some drawbacks to these methods are that they cannot definitively say that these cells are alive or whole, and as such we must be cautious of conclusions we draw.

Future Directions: Strategies to alter the fate and distribution of MSCs include altering their homing characteristics, decreasing MSC size, MSC injection directly at the site of injury, and prolonging their lifespan, offer considerable therapeutic potential. These strategies to enhance their function

will likely also effect on their movement and clearance in the body.

Summary and conclusions: MSCs are currently the focus of intense research to translate their very considerable potential for diverse clinical conditions into beneficial therapies. The COVID-19 pandemic has further focused attention on the immunomodulatory potential of MSCs. Modulating the distribution and fate of MSCs following therapeutic delivery constitutes a novel approach to further enhance their potential benefits. This area of research would be considerably enhanced by more robust approaches to tracking these intriguing cells within the human body.

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