

Immune modulation by extracellular vesicles released from mesenchymal cells

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Mesenchymal cells were described for their potency to interact with human immune cells and to modulate thereby immune responses. Besides mesenchymal stromal cells (MSC) from diverse tissue sources, like bone marrow and umbilical cord, also mesenchymal adherent cells within the heart tissue were able to attenuate and modulate induced immune cell activation or inflammatory processes. Mechanistic studies with MSC support the hypothesis, that mainly paracrine acting molecules, in particular extracellular vesicles (EVs), are responsible for the observed functional effects.

EVs are known as potent intercellular communicators by delivering proteins, lipids, RNA and other small signaling molecules to a recipient cell. They can be discriminated by their size and biogenesis into the subsets of apoptotic bodies (diameter > 1 μ m), microvesicles (diameter range = 1 - 0.1 μ m) and exosomes (diameter < 0.1 μ m). While microvesicles and apoptotic bodies are shedded from the plasma membrane, exosomes originate from intracellular located multivesicular bodies, which have to fuse with the plasma membrane for their release into the extracellular space. Crosstalk of EVs from MSCs with immune cells is a secured fact, but the way of up-take into the target cells and especially the mechanism of immune modulation are not entirely understood.

In our study, we isolated and characterized EVs from a human mesenchymal cardiac cell type regarding their potential to modulate induced immune responses in vitro. The presence of typical EV surface markers like tetraspanins (CD9, CD63, CD81) was confirmed as well as their low expression of HLA-molecules, which indicates a general low immunogenicity. Furthermore, EVs were able to attenuate triggered T cell proliferation accompanied by significantly reduced levels of pro-inflammatory cytokines (IFN γ , TNF α), which was highly dependent on the presence of CD14-positive cells. Interestingly, the EVs of cardiac mesenchymal cells induced a changed phenotype on these myeloid cells; most prominently a reduced HLA-DR and CD86 expression, but enhanced levels for CD206 and PD-L1.

Future studies have to identify key molecular pathways involved in EVs` crosstalk with immune cells and to estimate the benefits but also the risks of this new therapeutic based on mesenchymal cells.