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P778 Influence of the secretome of adipose-derived stem cells on M1 macrophages *in vitro*

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Introduction: Chronic wounds remain as a significant burden for patients and healthcare system. An important component in the pathogenesis of non-healing wounds is dysfunction of macrophages. In normal-healing wounds, the classically activated pro-inflammatory “M1” macrophages present at the early phases are replaced over time by alternatively activated “M2” macrophages, which stimulate angiogenesis and extracellular matrix deposition. However, most types of chronic wounds are characterized by persistence of the M1 phenotype. Strategies based on the use of mesenchymal stem cells (MSCs) have recently gained significant interest for the treatment of chronic wounds. In particular, accumulating experimental evidence suggests that MSCs favor the transition of M1 to M2 macrophages. These effects seem mostly mediated by paracrine factors secreted by the MSCs, including soluble factors and extracellular vesicles. However, the immunomodulatory role of the different components of the MSC secretome in the M1 to M2 transition remains largely unknown.

Aim: The aim of this study was to assess the effects of the different components comprising the MSCs secretome on M1 macrophages *in vitro*

Materials and methods: Cultured human adipose-derived stem cells (ASCs) were incubated in medium depleted of extracellular vesicles. The medium was harvested after 24 h and designated as the whole supernatant (WS). The WS was further divided into a soluble fraction (SF) and an extracellular vesicle (EV) fraction. The size and distribution of particles contained in the different fractions was determined by nanoparticle tracking analysis (NTA). M1 macrophages were obtained from the THP-1 human monocytic cell line after incubation in a pro-inflammatory cocktail. The M1 polarized cells were conditioned in the WS, SF or EV fraction for 48 h. The conditioned cells were labeled using antibodies against the CCR7 and CD163 receptors (as markers for M1 and M2 subtypes) and assessed by fluorescence microscopy. Additionally, qRT-PCR was used to assess the transcriptional activity of *CCR7* and *CD163* genes.

Results: While particles in the range of 40-180 nm (corresponding to exosomes and microvesicles) were found in the WS and EV fractions, no particles were detected in the SF fraction. Treatment with all three fractions attenuated the M1 phenotype, as evidenced by a decreased number of CCR7 and an increased number of CD163 positive cells. qRT-PCR analysis also revealed an anti-inflammatory effect from all three fractions, as evidenced by a significantly decreased transcription of CCR7 in the conditioned cells. However, only the WS and EV fractions significantly increased the transcriptional activity of CD163. These results suggest that the M1 to M2 transition appears to be mostly favored by components present in the EV fraction rather than in the SF counterpart.

Conclusions: Our results indicate that EVs released by MSCs may play an important role as mediators of their pro-inflammatory properties. MSC-derived EVs may therefore represent a novel cell-free treatment for non-healing wound conditions.