Tumor cell-derived small extracellular vesicles modulate macrophage immunosuppressive phenotype associated with PD-L1 expression

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Introduction: Tumour-associated macrophages (TAMs) play a key role in promoting tumour progression, by exerting an immunosuppressive phenotype associated with M2 polarization and with the expression of CD204 and programmed cell death ligand 1 (PD-L1). It is well known that tumour-derived extracellular vesicles (TEVs) play a pivotal role in the tumour microenvironment, influencing TAM behaviour. The study was aimed to examine the effect of TEVs derived from colon cancer and multiple myeloma cells on macrophage functions.

Methods: Non-polarized macrophages (M0) differentiated from THP-1 cells were co-cultured, for 3 up to 48 hours, with TEVs derived from a colon cancer cell line, SW480, and multiple myeloma cell line, MM1.S. The expression of M2 and TAM markers (respectively CD163 and CD204) as well as of PD-L1 and Interleukin 6 (IL6) were evaluated at mRNA and protein level. The apoptotic rate of CD3+ T cells cocultured with TEV-treated M0 macrophages was analysed by FACS.

Results: Our results indicate that TEVs can significantly upregulate the expression of surface markers of M2-like phenotype (CD163) and TAM (CD204) as well as of PD-L1, inducing macrophages to acquire an immunosuppressive phenotype. In parallel, we found that TEVs were also able to induce a significant increase of IL6 expression at both mRNA and protein levels and to activate the STAT3 signalling pathway. Since PD-1/PD-L1 axis is involved in the inhibition of T cells, we assessed the ability of macrophages treated with TEVs to affect T cell viability. We found that CD3+ T cells co-cultured with TEVs-treated M0 showed an increase of their apoptotic rate in comparison to CD3 + T cells grown in the presence of untreated macrophages.

Summary/Conclusion: Cumulatively, these preliminary data suggest that TEVs contribute to the immunosuppressive status of TAMs, promoting tumour growth and progression.

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