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Role of tumor-derived extracellular vesicles in immunosuppression in malignant melanoma patients

Autor: Xiaoying Hu
Institut / Klinik: Klinik für Dermatologie, Venerologie und Allergologie
Doktorvater: Prof. Dr. J. Utikal

The aim of the study was to investigate the role of extracellular vesicles (EVs) derived from human melanoma cell lines as well as from plasma of melanoma patients in conversion of circulating CD14+ monocytes into monocytic myeloid-derived (M-MDSCs). We demonstrated that EVs purified from melanoma cell line HT-144 (HT-144 EVs) showed an anti-apoptotic effect on CD14+ monocytes via the upregulation of Bcl-2 at the mRNA and protein level. Moreover, CD14+ monocytes showed a modulation in inflammatory gene expression as well as an enhanced migration activity upon HT-144 EV stimulation. Furthermore, upregulation of PD-L1 and downregulation of HLA-DR was observed in monocytes upon the treatment with EVs from HT-144 and another melanoma cell line SK-MEL-28, which confirmed the change of phenotype from classical monocytes to M-MDSCs. Importantly, the stimulated monocytes showed a strong immunosuppressive activity by inhibiting CD8+ T cell proliferation and the production of IFN-γ. The upregulation of PD-L1 was induced by via Toll-like receptor (TLR) signaling pathway, including TLR2 and TLR4, where TLR4 showed a prominent role. NF-□B was activated, which led to the upregulation of PD-L1. The blockage of TLR4 with anti-TLR4 blocking antibody or NF-□B with an NF-□B inhibitor significantly diminished PD-L1 upregulation. We also found that HSP86 was expressed on EVs from melanoma cell lines. By comparing monocytes stimulated with HSP86+ EVs with those from HSP86low/- EVs of HT-144 cells, we observed an abrogation of PD-L1 upregulation and immunosuppressive activity. Besides, we tested the expression of HSP86 on plasma EVs from melanoma patients responding and non-responding to anti-PD-1 therapy. We demonstrated that EVs from non-responders upregulated PD-L1 expression and induce immunosuppressive activity of circulating monocytes, converting them into M-MDSCs. In addition, those EVs displayed higher HSP86 expression as compared to non-responder EVs. Finally, we studied PBMCs from 30 melanoma patients before and after the treatment of anti-PD-1 therapy and found a significant decrease of PD-L1 expression in circulating monocytes from responders as compared to the level before therapy. Moreover, patients with lower PD-L1 expression on circulating monocytes showed better overall and progression free survival. Taken together, our finding demonstrated a crucial role of tumor-derived EVs in converting circulating monocytes into M-MDSCs and the importance of PD-L1 expression on monocytes in melanoma patients undergoing anti-PD-1 therapy for the prediction of therapy responsiveness.