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HSP90α induces immunosuppressive myeloid cells in melanoma via TLR4 signaling

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Tumor cells can modulate host immunity by secreting extracellular vesicles (EV) and soluble factors in the circulation. Uptake of these factors by myeloid cells or triggered signaling can lead to the generation of myeloid-derived suppressor cells (MDSC), which suppress anti-tumor activities of T and natural killer (NK) cells. Mouse and human melanoma-derived EV can induce this immunosuppressive activity by upregulating the expression of programmed cell death ligand 1 (PD-L1) on myeloid cells. This process was demonstrated to be dependent on the presence of heat-shock protein (HSP) 90α in EV and on toll-like receptor (TLR) signaling. It is known that EV-associated or cellular HSP90α could be a soluble serum compound. Here, we investigated whether HSP90α as a soluble factor can convert human monocytes into MDSC.

Cluster of differentiation (CD) 14 monocytes were isolated from the peripheral blood of healthy donors, incubated with human recombinant HSP90α (rHSP90α) and analyzed by flow cytometry. Inhibition of T cell proliferation assay was used to assess immunosuppressive function of rHSP90α-treated monocytes. Furthermore, levels of HSP90α were measured by ELISA in plasma of melanoma patients and correlated with clinical outcome.

We found that upon 16 h incubation with rHSP90α, monocytes strongly upregulated PD-L1 and indoleamine 2,3-dioxygenase 1 (IDO-1), while reactive oxygen species (ROS) and nitric oxide (NO) production, the expression of arginase-1 (Arg-1) as well as adenosine producing ectoenzymes CD39 and CD73 remained unchanged. The PD-L1 upregulation could be blocked by anti-TLR4 antibodies and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) inhibitor. After longer incubation (for 24h), rHSP90α-treated monocytes downregulated the expression of human leukocyte antigen DR isotype (HLA-DR). In addition, incubation with rHSP90α led to an increased viability and prevention of apoptosis. Monocytes treated for 24 h with rHSP90α acquired capacity to inhibit T cell proliferation in TLR4-, PD-L1-, and IDO-1-dependent manner. Higher levels of HSP90α in plasma of melanoma patients correlated with PD-L1 expression on blood-derived monocytic MDSC. Moreover, melanoma patients with higher levels of HSP90α receiving immunotherapy displayed shorter progression-free survival.

This thesis highlights a possible mechanism of monocyte conversion into MDSC by a soluble HSP90α, suggesting additional targets for overcoming immunosuppression in melanoma.