Immunosuppression in tumor microenvironment induced by chronic inflammation

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Melanoma is known for its poor response to current immunologic treatments. Insufficient anti-tumor reactivity could be due to the formation of a chronic inflammation represented by infiltrating leukocytes and soluble mediators, which lead to cancer progression. Using the ret transgenic mouse melanoma model that mimics human melanoma, we found in skin tumors and metastatic lymph nodes increased levels of inflammatory factors such as IL-1β, GM-CSF, and IFN-γ, which correlate with tumor growth. Moreover, Gr1+CD11b+ myeloid derived suppressor cells (MDSC) known to inhibit tumor reactive T cells were enriched in melanoma lesions and lymphatic organs during tumor progression. MDSC infiltration was associated with a strong TCR ζ-chain down-regulation. Co-culturing normal splenocytes with tumor-derived MDSC induced a decreased T cell proliferation and ζ-chain expression, verifying the MDSC immunosuppressive function. In addition to soluble chronic inflammatory mediators, tumor cells could induce immunosuppression by releasing of microvesicles (exosomes). We found that melanoma derived exosomes are able to convert Gr1+CD11b+ immature myeloid cells from normal mice into immunosuppressive cells producing high amounts of nitric oxide, expressing high arginase levels and being able to suppress T-cell proliferation.

Upon manipulation of the tumor microenvironment in melanoma bearing mice with the phosphodiesterase-5 inhibitor sildenafil, we observed reduced amounts of inflammatory mediators (IL-1β, VEGF, and GM-CSF) and immunosuppressive factors (nitric oxide and arginase-1) in association with decreased MDSC levels and immunosuppressive function. These led to the restoration of ζ-chain expression in T cells and to a significant increased survival of treated mice. In addition, the chemomodulation with very low, non-cytotoxic and non-cytostatic doses of paclitaxel also led to a substantial retardation of melanoma progression associated with an inhibition of chronic inflammatory mediator production in melanoma lesions and with a reduction of MDSC immunosuppressive activity. Our data suggest that inhibitors of the immunosuppressive tumor microenvironment induced by chronic inflammation should be applied in conjunction with melanoma immunotherapies to increase their efficacy.