Tumor-induced dysfunctions in adaptive and innate immunity: a novel therapeutic target for melanoma patients?

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Several molecular mechanisms are deemed responsible for the inability of the immune system to efficiently control tumor growth in primary or metastatic lesions, and for the reduced immunological and clinical responses to cancer vaccines. We recently characterized in cancer patients the phenotypic and functional features of myeloid-derived suppressor cells (MDSC), a key player in tumor-related immunsoppression. A major involvement of monocyte-like MDSC (moMDSC) expressing low level of HLA-DR and secreting TGF-beta along with a large panel of pro-angiogenic and pro-tumorigenic cytokines and chemokines, has been identified in melanoma patients. Interestingly, moMDSC accumulation can be detected in primary melanoma lesions and in peripheral blood of early stage melanoma patients, suggesting a crucial involvement of this pathway in disease progression. In contrast, we could not identify any sign of altered function in peripheral blood neutrophils, implying a limited impact of granulocyte-MDSC in melanoma. We are resently studing whether altered metabolic condition s affecting tumor site might also have relevant drawbacks on tumor immunity. Our data, obtained both in murine models and in cancer patients, clear show that low pH, an hallmark feature of tumor micro environment, enhances MDSC-mediated immunosuppression, while tumor pH buffering by the administration of proton pump inhibitors such as esomeprazole, readily reduces MDSC activity and allows T cell function recovery. Therefore, acidity of tumor micro environment represents a further mechanism of immune escape that can be overcome by drugs like PPI for recovering effective tumor immunity in cancer patients.