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Title: Splenectomy inhibits tumor development and metastases in murine lung cancer models

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Body: Introduction & Aims: It has been shown that inhibitors of the immune system (e.g. myeloid derived suppressor cells) reside in the spleen and inhibit the endogenous anti-tumor effects of the immune system. We hypothesized that excision of the spleen (splenectomy) can inhibit growth of relatively big tumors, and reduce metastases by modulating systemic inhibition of the immune system. Our long-term goal is to implement mechanisms elucidated in these studies into future clinical trials. Methods: The clinical effect of splenectomy was evaluated in several murine lung cancer models. We compared immunological properties of blood and tumor after splenectomy or sham operation in tumor-bearing mice, using FACS analysis, RT-PCR and specific depletion studies. Results: We found that splenectomy reduces tumor growth, can induce their regression, and decreases metastases. These effects disappeared in NOD/SCID mice. No significant changes in cell types were found in the blood. Splenectomy increased the percentage out of total tumor cells of neutrophils (2.4% vs. 4.9%, p=0.012), and macrophages (10.9% vs. 14.4%, p=0.014), which tended to be less immune-inhibitory (non-M2/M2 macrophages ratio increased from 3.4 to 12.1, p=0.04). We further noted a tendency to increased activation of $CD8^+$ CTL (19.2% vs. 30%, p=0.09). Tumor microenvironment was found to be more pro-inflammatory following splenectomy (e.g. upregulation of MIG, TNF-α and IFN-γ). Using specific depletion of cells we evaluated the role of each cell in the effect of splenectomy. Conclusions: Splenectomy inhibits the development of tumors and metastases in murine models of lung cancer, by changing the amount and characteristics of myeloid cells.