Vascular Normalizing Agents Differentially Modulate Tumor Cells, T Cells and Dendritic Cells in vitro

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Tertiary lymphoid structures (TLS) are lymph node-like structures that form at sites of inflammation, and their presence in cancer patients is predictive of a better clinical outcome. One significant obstacle to TLS formation is reduced immune cell infiltration into the tumor microenvironment (TME) as a result of an aberrant vasculature within the TME. Recent studies have shown that vascular normalizing (VN) agents may override this defect, leading to improved tissue perfusion and increased immune cell entry into the TME. However, the effects of VN agents on immune cell and tumor cell phenotype/function remain understudied. It was hypothesized that treating T cells and DCs with VN agents would induce a pro-inflammatory phenotype, while treating tumor cells would reduce their immunosuppressive phenotype and promote production of chemokines that foster TLS formation. To test this, a BPR melanoma cell line and primary murine T cells and DCs were treated overnight with VN agents. The next day, samples of treated and untreated cells of each cell type were harvested for analyses to measure transcript levels of target genes as well as relative frequencies of cell surface markers. Treatment of tumor cells lead to increased TLS production of TLS-promoting factors. While Aduro and Bevacizumab were strongly and weakly immunostimulatory for T cells respectively, Dasatinib was predominantly immunosuppressive. Meanwhile, VN agents decreased MHC and co-stimulatory molecule expression on DCs but increased TLS promoting chemokine transcript levels. Overall, VN agents have differential effects on immune and tumor cell phenotype. Future experiments will analyze immunomodulatory effects within the TME in vivo to further determine optimal immunotherapy designs in the cancer setting.

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