BLOCKADE OF VEGF, ANGIOPOIETIN-2, AND PD1 REPROGRAMS DYSFUNCTIONAL ENDOTHELIAL CELLS IN GLIOBLASTOMA TO QUASI-ANTIGEN-PRESENTING CELLS

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Background Glioblastoma (GBM) is the most aggressive and deadly primary tumor. Endothelial cells (ECs) in GBM vessels form a barrier between circulating immune cells and parenchymal tissue. ECs in GBM are dysfunctional, conferring resistance to immunotherapy. Anti-VEGF-induced vascular normalization is insufficient to fully restore the EC function. Our studies and others have shown that antiangiogenic agents inhibiting VEGF signaling can transiently restore normal vascular function and thus significantly increase infiltration of cytotoxic T cells (CTLs). However, CTL accumulation in the tumor bed is necessary but not sufficient for the therapeutic response. Sustained activation of CTLs by antigen-presenting cells is a key step for effective antitumor responses.

Methods Using three orthotopic preclinical GBMs, ex vivo and in vitro studies, we investigated whether reprogramming the dysfunctional GBM ECs upregulates receptors on ECs that promote CTL trafficking, reprogrammed ECs present tumor antigens to CTLs, and this antigen presentation results in generation of an active tumor-immune niche in GBM.

Results Concomitant blockade of Ang2, VEGF using a bispecific antibody (A2V), and aPD1 reprograms dysfunctional endothelial cells to quasi-antigen-presenting cells and upregulates receptors required for cytotoxic T lymphocyte entry into the tumor. Blocking VEGF, Ang2, and PD1 induces durable anti-tumor T cell response in preclinical GBM models. Upregulation of the transcription factor T-bet is both necessary and sufficient for generating resident memory T cells elicited by this therapeutic regimen (figure 1).

Conclusions Collectively, our data (i) provide heretofore unknown insights into targeting Ang2 as a shared resistance pathway for both aVEGF and aPD1 in experimental GBM models, (ii) demonstrate a strategy to reprogram ECs to activate and promote CTL recruitment into GBMs followed by retaining intratumoral T cells, (iii) offer a possible solution to overcome GBM resistance to aVEGF and aPD1, and (iv) provide mechanistic insights into how T cell memory forms after aPD1+A2V therapy. Multiple strategies to combine aPD1 and aVEGF are currently being evaluated in clinical trials for non-CNS tumors, and our study provides a foundation for testing the combination of a more effective vascular normalizer A2V in combination with aPD1/PD-L1 in GBM patients where aPD1 monotherapy and in combination with aVEGF+aPD1 have failed in all randomized clinical trials.

REFERENCES