Blocking Immunosuppressive Checkpoints for Glioma Therapy: The More the Merrier!

Maria G. Castro, Gregory J. Baker, and Pedro R. Lowenstein

Immunosuppressive checkpoints mediated by IDO, CTLA4, and PD1/PDL1 play a critical role in glioma progression and the efficacy of immunotherapies. Combined blockade of these immunosuppressive checkpoints in a glioma model elicited long-term survival. This combined blockade adds to the armamentarium of anti-glioma therapies, which could be implemented in clinical trials. Clin Cancer Res; 20(20); 5147–9. ©2014 AACR.

In this study, the authors targeted the inhibition of IDO in combination with therapies aimed at inhibiting CTLA4 and PD1/PDL1 function to develop an effective immune therapeutic strategy for the treatment of glioma, a strategy that could be potentially translated to human clinical trials (Fig. 1). To inhibit IDO, the authors used the tryptophan analog, 1-methyltryptophan (1-MT), an IDO-specific competitive inhibitor that blocks L-tryptophan conversion to N-formyl-kynurenine and thus prevents Treg accumulation in the tumor microenvironment. The authors inhibited CTLA4 using anti-CTLA4 monoclonal antibodies, which bind to CTLA4, inhibiting its immunosuppressive activity, while freeing up CD80 and CD86 to bind to CD28, a T cell–activating receptor. The third immune checkpoint targeted by the authors is the PD1–PDL1 axis. Malignant glioma cells express PDL1, which interacts with its cognate receptor programmed death 1 (PD1) on the T-cell surface to downregulate tumor lytic capacity and promote T-cell anergy in the context of tumor antigen–presenting MHC class I molecules. Anti-PDL1 monoclonal antibodies bind to PDL1 on
the surface of tumor cells, thus enabling T cells to remain activated, with high tumor lytic capacity and T-cell proliferation. The survival data presented by the authors in the glioma model indicate that the combined triple immunosuppressive checkpoint blockade provides maximum efficacy when compared with monotherapies using 1-MT, anti-CTLA4, or anti-PD1 alone or when compared with blockade of two immunosuppressive checkpoints (1). The data shown indicate that blockade of the inhibitory CTLA4 and PD1/PDL1 costimulatory pathways in combination with IDO inhibition, to decrease levels of Tregs in the tumor microenvironment, enables anti–tumor-specific effector T cells to continue to expand and display potent cytotoxic effector functions. Interestingly, when testing the triple combined blockade in a model of aggressive intracranial melanoma, the overall survival benefit was days, as opposed to months as observed in the glioma model. The authors hypothesize that the triple combination blockade would be more effective in tumors that exhibit highly prevalent immunosuppressive characteristics, i.e., glioma as opposed to tumors that evade antitumor immune responses using alternative mechanisms (1). These results also highlight the role that different tumor types exert to subvert antitumor immunity and reinforce the importance of testing novel therapies in the most relevant in vivo models before implementation in the clinic.

To date, several immune-stimulatory approaches have been proposed for treating glioma, and many of these have been tested in the clinic with some indication of biologic activity. These include vaccination strategies using dendritic...
cells, specific peptide tumor antigens, and engineered T cells (12). Nevertheless, these immune-stimulatory activities have not yet been translated into increased median survival in the glioma patient population. The report by Wainwright and colleagues is the first to test the combined blockade of three critical immunosuppressive checkpoints, IDO, CTLA4 and PD1/PDL1; the data reported indicate that the approach is highly effective, yielding a robust decrease in tumor-infiltrating Tregs concurrent with tumor regression, long-term survival (measured in months’), and immunologic memory in a relevant glioma model. Interestingly, another multipronged immunologic approach for glioma, pioneered by our group (2) also achieves survival that can be measured in months in a comparable model, and is currently being tested in a phase I clinical trial for glioma. We anticipate that the approach proposed by Wainwright and colleagues could be translated into phase I clinical trials for glioma in the near future, as these approaches have already been used individually in patients suffering from systemic tumors and clinical grade reagents are readily available. In addition, the data reported highlight that for immunotherapies to succeed, multiple pronged strategies are key.

References

Clinical Cancer Research

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