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Letter to the Editor

The Sybil prophecy: Searching for predictors of response to bevacizumab in glioblastoma

We read with great interest the work by Hiller-Vallina et al.[1] on the role of a sexual-dependent necroinflamed pattern in predicting prognosis and response to anti-angiogenic drugs in glioblastoma. The work has huge strong points, including its elegant and meticulous design, and also opens a number of issues. Female gender has not traditionally been recognized as a positive prognostic factor in glioblastoma, yet evidence is rising that this assumption is true. In the present paper, Hiller-Vallina et coworkers demonstrate that, in a subset of male patients, low levels of estrogen receptor-α (encoded by ESR1 gene) determine a necroinflamed phenotype, with activation of VEGF/hypoxia-related pathways and infiltration of S100A9-positive myeloid cells. Male patients harboring low-ESR1 necroinflamed glioblastomas have a worse prognosis than male and female patients harboring high-ESR1 non-necroinflamed tumors. On the other hand, necroinflamed tumors show a better response to anti-angiogenic treatment. Much work remains to be done to dissect into detail the relationship between sex hormones, tumor immune infiltration and hypoxic/angiogenic microenvironment. Our research group recently investigated the prognostic role of the immune infiltrate in glioblastoma, with focus on the tissue-resident memory (Trm) CD8 + CD103 +T lymphocytes, finding that high levels of Trm expressing PD1 or other immune checkpoints are correlated to worse prognosis, likely due to immune cell exhaustion.[2] We reanalyzed survival data of patients included in that study and, interestingly, we found that the proportion of exhausted CD8 + CD103 + PD1 +Trms portends a worse prognosis only in male patients (Figure 1). Such finding corroborates the assumption by Hiller-Vallina et al. on the existence of two distinct subsets of GBM in males, with different prognosis.[1] Notably, PD1 expression on Trm has been linked to persistent neuroinflammation in encephalitis,[3] further supporting the assumption that immune-exausted Trms can be enriched in necroinflammed glioblastoma. The issue of the improved response of male patients with necroinflamed glioblastoma to anti-angiogenic treatment with bevacizumab is more puzzling. Interestingly, no consistent predictors of response to bevacizumab in glioblastoma have been ever established. A post-hoc analysis of the AVAglio trial identified the proneural signature as associated with better response to bevacizumab.[4] However, it is well known that the expression of

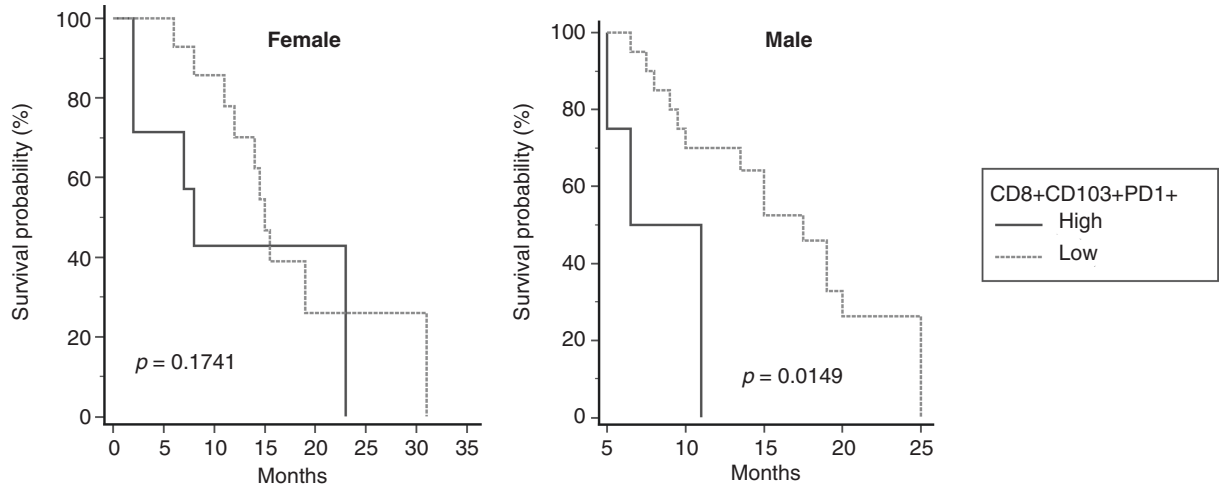

Figure 1. Kaplan-Meier survival curves of the 45 glioblastoma patients reported in Ref.,[2] based on levels of exhausted CD8 + CD103 + PD1 + Trms. *Left,* female gender. *Right,* male gender.

inflammation-related players is downregulated in proneural and upregulated in mesenchymal glioblastoma, in contrast with the findings of the present study.[5] The role of VEGF expression is also debated. Hiller-Vallina et al[1] reported that necroinflamed glioblastoma upregulated VEGF, yet VEGF levels as assessed with RT-PCR were not associated with improved survival after bevacizumab treatment. Instead, in a work on 25 recurrent GBM patients, we had shown that high VEGF levels were associated with worse survival after bevacizumab treatment in recurrent glioblastoma.[6] To conclude, the work here discussed has the merit to enliven the interest of the neuro-oncologic community on the interplay between gender and immune infiltrate in glioblastoma and on the identification of prognostic factors for response to anti-angiogenic treatment, which are long awaited.

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