RESEARCH HIGHLIGHT

Neutralizing shapeshifting pericytes enhances glioblastoma therapeutic efficacy

Samuel A. Sprowls^{1,2} and Justin D. Lathia^{2,3,4}✉

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Cell Research (2021) 31:1039–1040; <https://doi.org/10.1038/s41422-021-00538-1>**Maraviroc, an FDA-approved therapy, provides a potentially viable treatment option for those diagnosed with glioblastoma harboring a high amount of pericyte support cells.**

Glioblastoma (GBM) is the most common primary malignant brain tumor, and prognosis remains poor, with a median survival of < 16–20 months¹. Conventional therapeutic interventions for GBM, including radiation and non-specific chemotherapeutic treatments, are designed to target tumor cells and their intrinsic signaling programs rather than to influence various cell types in the surrounding microenvironment. Refocusing the intended target of therapeutic strategies to cell-extrinsic mechanisms in the surrounding tumor microenvironment and the molecular interactions between GBM cells and surrounding cells has provided a crucial framework for novel treatment strategies and future discoveries².

Zhang and colleagues have investigated the role of pericytes, which are extravascular support cells that regulate a wide array of physiological functions and pathological development of the blood–tumor barrier (BTB)^{3,4}, and the differential expression of a key signaling molecule, CCL5, in temozolomide (TMZ)-responsive and TMZ-resistant tumors⁵. The authors found increased pericyte markers in a subset of TMZ-resistant GBM patients, and expression of these markers was associated with a worsened outcome and more aggressive tumor independent of vascular density. Similarly, the proximity of tumor cells to pericytes in human GBM samples informed the degree of response to TMZ therapy.

In a second set of experiments, genetic depletion of pericytes from mouse xenograft models of GBM improved response to treatment with TMZ but did not increase the penetration of TMZ beyond the BTB. Additional experiments using validated, isolated human GBM pericytes demonstrated that pericytes indeed influence the response of GBM cells to TMZ in vitro. Additionally, the same resistance potential was observed with pericyte conditioned media. These data indicated that the mechanism by which pericytes induce TMZ resistance in pericyte^{high} tumors is linked to a paracrine signaling mechanism involving a soluble factor.

Further in vitro analyses demonstrated a role for CCL5, which was found to be highly upregulated in isolated GBM-associated pericytes. Knockdown or pharmacological inhibition of CCL5 increased the sensitivity of GBM cells treated with pericyte conditioned media to TMZ. Similarly, the CCL5 antagonist

maraviroc (MVC) restored the sensitivity of GBM cells treated with pericyte conditioned media to TMZ. Taken together, these results indicate that the use of a known CCL5 antagonist is capable of reversing pericyte-induced TMZ resistance. Taking the same approach in in vivo preclinical animal studies showed similar results. Mice treated with both TMZ and MVC show a statistically significant decrease in tumor size and increase in survival compared to vehicle control and either agent alone. Molecularly, treatment with both TMZ and MVC increased the amount of γ -H2AX and decreased the amount of p-DNA-PKcs, two entities involved in the DNA damage response (Fig. 1). These data inform two thoughts: (1) treatment with MVC restores TMZ sensitivity in vivo and (2) the downstream mechanism of MVC decreases DNA damage response and sensitizes pericyte^{high} tumor cells to TMZ in vivo.

Lastly, the group correlated pericyte^{high} and pericyte^{low} with progression-free survival. A longer progression-free survival was observed in the pericyte^{low} patients compared to pericyte^{high} patients. These data were well correlated with both CCL5 and CD146 expression. Using an informed patient-derived xenograft model of high and low pericyte involvement, the group showed the ability to reduce tumor size after a 3-day cycle of TMZ, followed by a 3-day cycle of TMZ and MVC. The combined therapeutic approach in pericyte^{high} mice was similar to TMZ-treated pericyte^{low} mice. These data suggests that pericyte involvement can be used as a prognostic marker and inform treatment strategies from a precision medicine standpoint in humans.

The studies in this paper interrogate the utility of MVC in pre-clinical GBM models. MVC and other CCL5-CCR5 pathway inhibitors are also undergoing clinical evaluation for multiple tumor types⁶. The CCL5-CCR5 signaling axis has been studied extensively and contributes to tumor progression both by direct effects on proliferation and by indirect induction of angiogenesis and recruitment of immune cells to the GBM microenvironment^{7,8}. For this reason, inhibition of CCL5-CCR5 may be leveraged for not only pericyte targeting but also for other pro-tumorigenic processes. Importantly, MVC is well suited for use in primary brain tumors (such as GBM) due to its favorable toxicological profile and ability to pass through the BTB. While the current study investigated the ability of MVC to inhibit CCL5 from binding to the CCR5 receptor on GBM cells, MVC is also capable of inhibiting other cancer properties, including metastasis and invasion. Other

¹Department of Basic Pharmaceutical Sciences, School of Pharmacy, Health Sciences Center, West Virginia University, Morgantown, WV, USA. ²Department of Cardiovascular & Metabolic Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA. ³Rose Ella Burkhardt Brain Tumor & Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH, USA. ⁴Case Comprehensive Cancer Center, Cleveland, OH, USA. ✉email: lathiaj@ccf.org

Fig. 1 High pericyte populations in GBM provide a CCL5-CCR5 mediated TMZ resistance pattern, reversible by treatment with MVC. CCL5 secreted by pericyte support cells in the GBM tumor microenvironment induces activation of DNA damage repair response as a resistance mechanism to treatment with TMZ (left). Treatment with MVC blocks receptor binding of CCL5 to its cognate receptor, decreasing p-DNA-PKcs and increasing γ H2AX and sensitizing GBM cells to TMZ (right).

groups have analyzed gene expression programs in GBM pericytes and found that pericytes are involved in the transition of low-grade to high-grade glioma, thus showing the importance of targeting support cells for novel treatment modalities⁹. In the larger context of treatment strategies, this study highlights the advantage of repurposing approved therapeutics for initial assessments in pre-clinical experiments to inform future clinical trials and provide a fast track for potentially improved outcomes in cancer patients.

REFERENCES

- Weller, M. et al. *Lancet Oncol.* **18**, 1373–1385 (2017).
- Lathia, J. D., Mack, S. C., Mulkearns-Hubert, E. E., Valentim, C. L. & Rich, J. N. *Genes Dev.* **29**, 1203–1217 (2015).
- Cheng, L. et al. *Cell* **153**, 139–152 (2013).
- Zhou, W. et al. *Cell Stem Cell* **21**, 591–603 (2017).
- Zhang, X. N. et al. *Cell Res.* <https://doi.org/10.1038/s41422-021-00528-3> (2021).
- Jiao, X. et al. *Cancer Res.* **79**, 4801–4807 (2019).
- Takacs, G. P., Flores-Toro, J. A. & Harrison, J. K. *Pharmacol. Ther.* **222**, 107790 (2021).
- Yu-Ju Wu, C. et al. *Neuro. Oncol.* **22**, 253–266 (2020).
- Oudenaarden, C., Sjolund, J. & Pietras, K. *Mol. Oncol.* <https://doi.org/10.1002/1878-0261.13016> (2021).

ADDITIONAL INFORMATION

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