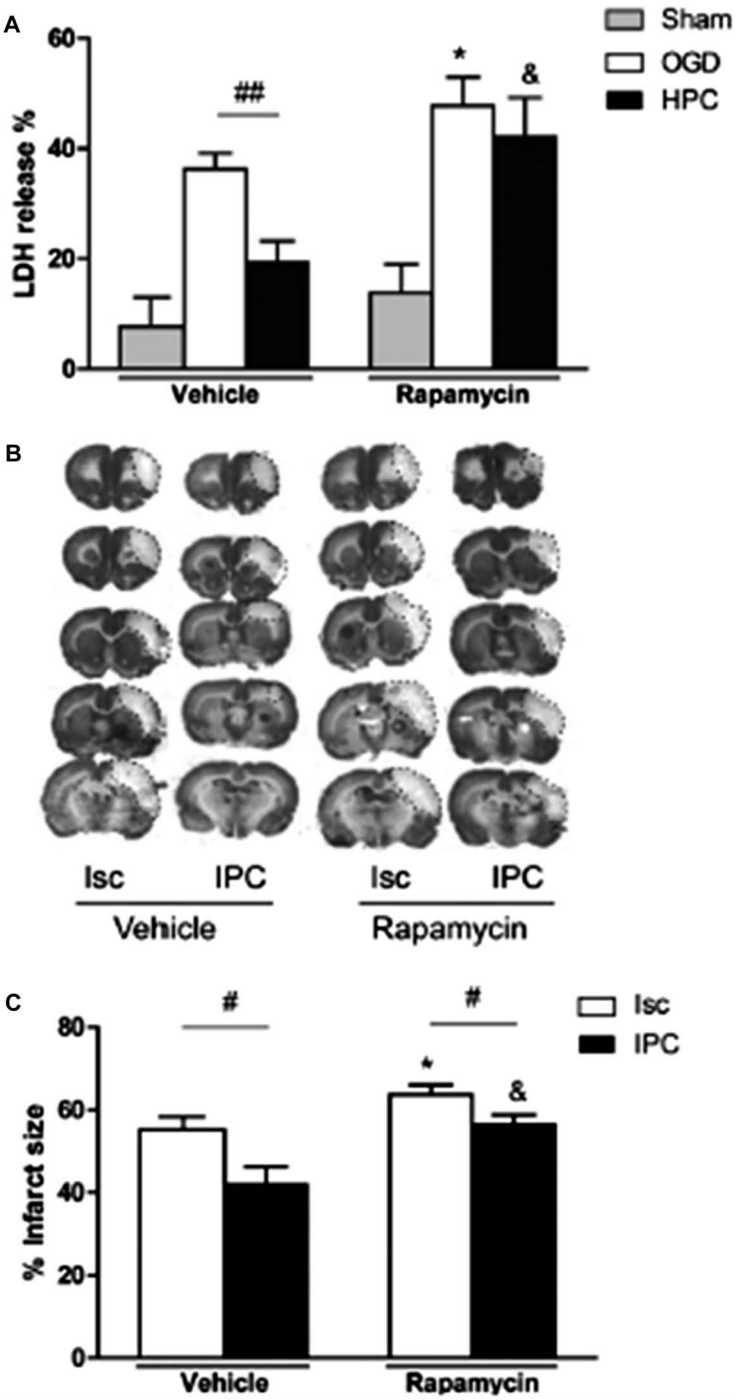

Figure. Rapamycin blocked the neuroprotective effects of hypoxic postconditioning (HPC) and ischemic postconditioning (IPC) both in vitro and in vivo. **A**, *effects of rapamycin and HPC on neuronal death as measured by lactate dehydrogenase (LDH) release in vitro. LDH release was measured 18 hours after oxygen-glucose deprivation (OGD). All data from cultures with OGD were normalized to the values of control, non-OGD samples treated with vehicle that did not contain rapamycin (n = 16 per group).* **B**, *representative coronal sections of ischemic brain stained by the cresyl violet method. Infarct regions are traced.* **C**, *average infarct sizes measured from 5 coronal sections (n = 8 per group). *P <.05 vs the vehicle of the indicated group; #P < .05, ##P < .01 between the 2 indicated groups.* Reprinted with permission from Xie et al.[5]

REFERENCES

1. Zhao H. Ischemic postconditioning as a novel avenue to protect against brain injury after stroke. *J Cereb Blood Flow Metab.* 2009;29(5):873-885.
2. Zhao H, Sapolsky RM, Steinberg GK. Interrupting reperfusion as a stroke therapy: ischemic postconditioning reduces infarct size after focal ischemia in rats. *J Cereb Blood Flow Metab.* 2006;26(9):1114-1131.
3. Pignataro G, Meller R, Inoue K, et al. In vivo and in vitro characterization of a novel neuroprotective strategy for stroke: ischemic postconditioning. *J Cereb Blood Flow Metab.* 2008;28(2):232-241.
4. Jewell JL, Guan XL. Nutrient signaling to mTOR and cell growth. *Trends Biochem Sci.* 2013;28(5):233-242.
5. Xie R, Wang P, Cheng M, Sapolsky R, Ji X, Zhao H. Mammalian target of rapamycin cell signaling pathway contributes to the protective effects of ischemic postconditioning against stroke. *Stroke.* 2014;45(9):2769-2776.

A Previously Unidentified Mechanism of Immune Evasion in Glioblastoma

Despite gradual advancements in surgical technique, chemotherapy, and radiotherapy, current treatments for glioblastoma multiforme (GBM) still have only limited efficacy.[1] One evolving strategy is the development of immunotherapies that upregulate or activate host immune function to target and destroy GBM cells.[2] There is evidence, however, that patients with GBM have suppressed immune function, which may limit the success of immunotherapy.[3]

Natural killer (NK) cells, an important component of the innate immune system, typically express NKG2D receptors on their cell surface. These receptors bind specific ligands (eg, MICB, ULBP-1) on target cells of interest, and binding triggers the release of cytotoxic granules and inflammatory cytokines, ultimately causing target cell death. Interestingly, it has been observed that NK cells have downregulated the expression of NKG2D in patients with GBM.[4]

Myeloid-derived cells, including circulating monocytes and tumor-infiltrating macrophages, are believed to be an important driver of tumor-mediated immune invasion.[5] Crane et al[6] recently studied myeloid-lineage cells from patients with GBM and found that these cells overexpressed the NKG2D ligands MICB and ULBP-1 on their cell surfaces compared with myeloid cells from control subjects without GBM.

Next, the investigators studied several GBM cell lines (U87, SF767, U251) and determined that both lactate dehydrogenase 5 (LDH5), a tetrameric metabolic enzyme produced by

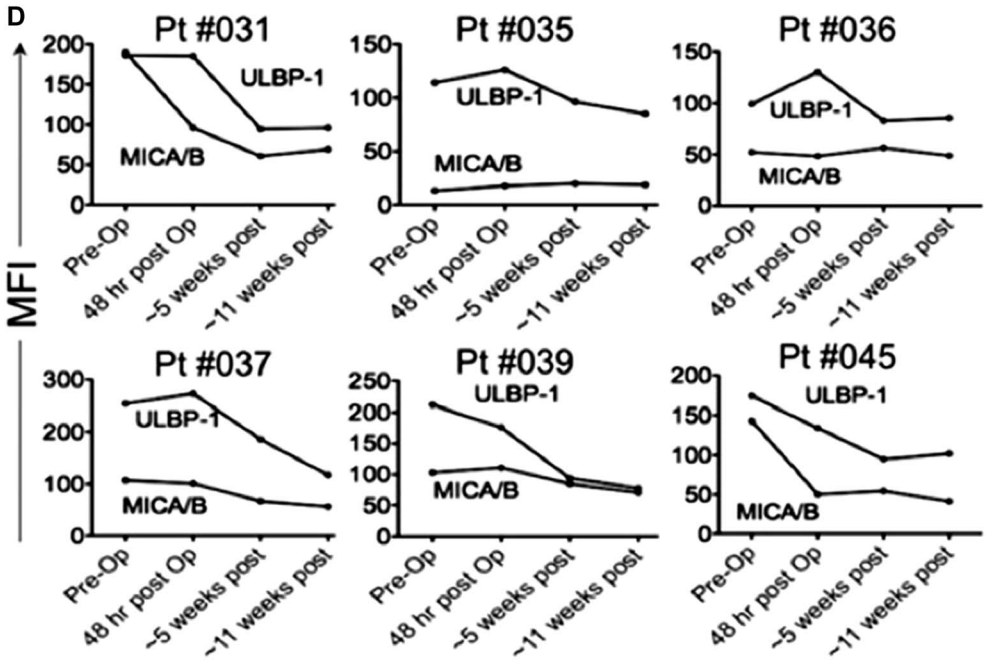

Figure. Longitudinal analysis of the expression of NKG2D ligands MICA/B and ULBP-1 using flow cytometry on circulating monocytes in recurrent glioblastoma multiforme patients after tumor resection. Note the trend toward decreasing ligand expression after surgical resection. Adapted from Crane et al.[6]

GBM cells, and its substrate pyruvate were necessary to induce MICB and ULBP-1 expression in these myeloid cells. They exposed myeloid cells simultaneously to LDH5 and sodium oxalate (a molecule that specifically blocks LDH activity) and showed reduced ligand expression. They showed that the LDH5 content of sera from GBM patients induces myeloid cell ligand expression at a significantly higher rate than sera taken from those same patients 33 days after gross total tumor resection (Figure).

The study suggests that GBM production of LDH5 induces NKG2D ligand expression on host myeloid-derived cells, which likely attenuates NKG2D expression on NK cells.[7] Future research should define the mechanisms by which LDH5 alters myeloid cell protein expression and the mechanisms by which expression of ligands modulates NKG2D function and expression on NK cells. Myeloid-derived cell ligand expression could be studied as a potential biomarker of disease recurrence. The ability of LDH5 inhibitors to counteract the proposed mechanism of tumor-induced immunosuppression should be explored. The authors are congratulated for this important study, which describes a previously unidentified mechanism for immune evasion in GBM patients.

Benjamin M. Zussman, MD
Christopher P. Deibert, MD
Johnathan A. Engh, MD
University of Pittsburgh
Pittsburgh, Pennsylvania

REFERENCES

1. Kawano H, Hirano H, Yonezawa H, et al. Improvement in treatment results of glioblastoma over the last three decades and beneficial factors. *Br J Neurosurg.* 2014. doi:10.3109/02688697.2014.967750. Available at: http://informahealthcare.com/doi/abs/10.3109/02688697.2014.967750.
2. Thomas AA, Brennan CW, Deangelis LM, Omuro AM. Emerging therapies for glioblastoma. *JAMA Neurol.* 2014;71(11):1437-1444.
3. Rabinovich GA, Gabrilovich D, Sotomayor EM. Immunosuppressive strategies that are mediated by tumor cells. *Annu Rev Immunol.* 2007;25:267-296.
4. Crane CA, Han SJ, Barry JJ, Ahn BJ, Lanier LL, Parsa AT. TGF-beta downregulates the activating receptor NKG2D on NK cells and CD8+ T cells in glioma patients. *Neuro-oncology.* 2010;12(1):7-13.
5. Diaz-Montero CM, Finke J, Montero AJ. Myeloid--derived suppressor cells in cancer: therapeutic, predictive, and prognostic implications. *Semin Oncol.* 2014;41(2):174-184.
6. Crane CA, Austgen K, Haberthur K, et al. Immune evasion mediated by tumor-derived lactate dehydrogenase induction of NKG2D ligands on myeloid cells in glioblastoma patients. *Proc Natl Acad Sci U S A.* 2014;111(35):12823-12828.
7. Coudert JD, Zimmer J, Tomasello E, et al. Altered NKG2D function in NK cells induced by chronic exposure to NKG2D ligand-expressing tumor cells. *Blood.* 2005;106(5):1711-1717.