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. One evolving strategy is the development of immunotherapies that upregulate or activate host immune function to target and destroy GBM cells. There is evidence, however, that patients with GBM have suppressed immune function, which may limit the success of immunotherapy.

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.

Myeloid-derived cells, including circulating monocytes and tumor-infiltrating macrophages, are believed to be an important driver of tumor-mediated immune invasion. Crane et al 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...
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. 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.

**REFERENCES**