Monocarboxylate transporter

Monocarboxylate transporters (MCTs) are a family of membrane proteins that mediate the transport of monocarboxylates such as lactate, pyruvate, and ketone bodies across the plasma membrane, often coupled with H^+ ions. These transporters are essential for maintaining intracellular and extracellular pH homeostasis and supporting metabolic adaptation, particularly under hypoxic and glycolytic conditions common in malignant tumors.

 MCTs in Glioma Pathobiology

 Key Isoforms: MCT1 (SLC16A1): High affinity for lactate, expressed in both oxidative and glycolytic cells.

MCT4 (SLC16A3): Low affinity but high capacity, induced by hypoxia-inducible factor 1 (HIF-1α) and upregulated in highly glycolytic, hypoxic tumors.

MCT2 (SLC16A7): Highest affinity for lactate, recently recognized for its nuanced regulation in astrocytes and glioma cells in response to pH, hypoxia, glucose, and lactate, as shown by Caruso et al. [1].

 Molecular Functions in GBM: Glioblastoma (GBM), the most aggressive primary brain tumor, exhibits a hallmark aerobic glycolytic phenotype (Warburg effect), leading to excessive lactate production. MCT1 and MCT4 mediate lactate efflux to prevent “self-poisoning,” facilitating:

Tumor cell survival under metabolic stress

Invasion of surrounding tissue

Immune evasion via acidic microenvironment

 Relevance in Neurosurgical Practice 1. Tumor Aggressiveness & Surgical Planning High MCT1/4 expression correlates with aggressive tumor biology in GBM [2]

Their presence may mark invasive margins or hypoxic cores, which are difficult to resect and more likely to recur. Future intraoperative imaging (e.g., hyperpolarized MRI or pH-sensitive probes) may enable visualization of metabolically active MCT-rich zones to optimize resection margins.

2. Pathological Diagnosis and Immunohistochemistry MCT1/4 immunoreactivity can aid in distinguishing IDH-wildtype GBM from lower-grade gliomas when molecular data is incomplete. Pathologists and neurosurgeons may use MCT staining to infer tumor grade, prognosis, and potential therapeutic vulnerability.

3. Adjunctive Therapies Post-Resection Targeting MCTs offers a metabolism-based adjuvant approach.

Syrosingopine, a dual MCT1/4 inhibitor with CNS penetration, demonstrates apoptotic and anti-invasive effects in glioma cell lines and is a candidate for clinical repurposing.

Combined therapies (e.g., with metformin) may synergize to exhaust tumor metabolic plasticity.

4. Neurosurgical Research and Innovation MCTs are a valuable focus in translational neuro-oncology:

Biopsy targeting, tumor banking, and delivery of MCT inhibitors (e.g., via convection-enhanced

delivery) are emerging research avenues.

Understanding the pH-lactate-hypoxia interplay via MCT regulation (as described by Caruso et al.) may lead to new molecular imaging markers or pH-responsive delivery systems.

⚠ Current Limitations

No MCT-targeting therapy is yet approved for clinical neurosurgical use.

Expression heterogeneity within tumors and across patients complicates therapeutic targeting.

Isoform-specific inhibitors with safe CNS profiles are needed.

Non-invasive radiological detection of MCT activity is still under development.

Clinical Takeaway for Neurosurgeons

Monocarboxylate transporters—particularly MCT1 and MCT4—are more than molecular curiosities; they are critical markers and mediators of glioma aggressiveness. Their expression informs diagnosis, surgical planning, and offers a metabolic Achilles' heel that could be exploited through adjuvant therapy. As glioma therapy moves toward precision medicine, MCTs represent a bridge between metabolic biology and neurosurgical practice.

References

1)
Caruso JP et al. pH, Lactate, and Hypoxia: Reciprocity in Regulating High-Affinity Monocarboxylate Transporter Expression in Glioblastoma. Neoplasia. 2017;19(2):121-134. doi: 10.1016/j.neo.2016.12.011.
2)
Behera MM et al. The Monocarboxylate Transporters MCT1 and MCT4 Are Highly Expressed in Glioblastoma and Crucially Implicated in the Pathobiology. Neuropathology. 2025 Mar 27. doi: 10.1111/neup.70006. PMID: 40145253.