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# V-ATPase expression in gliomas—Not your grandparents' proton pump

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Brain tumors such as the high-grade gliomas (HGGs; grade III and IV, the latter called "glioblastomas" or GBMs) are horrid cancers with abysmal prognoses; median survival for patients afflicted with GBMs remains <15 months despite standard-of-care interventions (surgery, chemotherapy, radiation), which has changed little in the past 15 years [1]. One thing that has changed during this period is the way pathologists categorize gliomas (and other brain tumors) based on histopathology, but now combined with molecular/genetic markers [2]. Among the most important new markers, particularly for adult low-grade (grade II) gliomas (LGGs), are mutations in the genes encoding isocitrate dehydrogenase isoforms 1 and 2 (*IDH1/2*) [3], where patients with LGGs (and also HGGs) bearing *IDH* mutants show longer survival compared to patients having tumors with wild-type status. The cellular biochemical/metabolic consequences of such mutations are complicated, and how this relates to the prolonged survival in gliomas is unclear [4]. Nonetheless, the wild-type *IDH* status often yields a more HGG-like prognosis, ie, low-grade tumors with a natural history more like high-grade tumors, but there is broad heterogeneity of overall survival within that LGG class [5]. The search for other molecular markers and clinical indicators to differentiate LGGs that do not need aggressive therapy (and the debilitating effects from that) *vs* LGGs that should be treated like HGGs (with intense therapy to prolong survival) is a hot area of research in neuro-oncology.

As recently published in *EBioMedicine* [6], Andrea Terrasi and colleagues investigated the subunit content of the proton pump vacuolar ATPase (V-ATPase) across GBMs (including studies in a *Drosophila* model), and extending into database analyses across LGGs and HGGs. V-ATPase is a multi-subunit, membrane-embedded protein complex that utilizes ATP to pump protons across intracellular and extracellular membranes. The $V_1$ sector possesses ATP hydrolytic capacity, generating torque to rotate the central stalk, allowing passage of protons across the $V_0$ membrane domain. The 13 subunits and some 30 polypeptides comprising the enzyme complex form a veritable "alphabet soup" of nomenclature, with differential subunit expression defining subcellular localization and tissue specificity; dysregulation of expression and localization are frequently seen in cancers [7]. Despite some 4000+ entries in PubMed, V-ATPase is a very under-studied entity in brain tumors. The group here shows that V-ATPase subunit composition correlates to aggressiveness in patient-derived GBM cells grown as "neurospheres" under stem cell-like or de-differentiated conditions. This prompted genetic experiments in a *Drosophila* larvae model (which certainly shows unique potential for screening of genetic interactions and drug treatments [8]); those were followed by intracranial xenograft studies in mice, all demonstrating that $V_1$ subunit differences have *in vivo* relevance for tumor growth and invasiveness.

The authors extended the V-ATPase subunit expression studies across gliomas and into LGGs with wild-type or mutated *IDH1/2* to develop possible patterns of expression correlating with tumor grade, *IDH* mutation status, and other differentially-expressed genes. They evaluated three datasets (TCGA, Gravendeel, and an in-house cohort), and in the end, determined that expression levels of three V-ATPase subunits (*ATP6V1G2*, *ATPV0A1*, and *ATPV1C1*–and probably upregulation of *ATPV1G1* [Uniprot designations]) could implicate more HGG-like outcomes for patients with LGGs that were wild-type for *IDH*. Those tumors acted like higher grade tumors, considering their pathologic designations. The group added in the likelihood that certain homeobox (HOX) genes *HOXA7*, *HOXA10*, *SHOX2*, and *POU3F2* were related to the de-differentiation profiles (or stem cell-like expression patterns) associated with the more GBM-like LGGs (and validated this in the *V1G1* high/*V1G2* low-expressing GBM neurospheres). Thus, de-differentiation, a known factor in the GBM subclassification, relates to subunit changes in the V-ATPase.

While the relationships with the HOX genes has yet to be elucidated, the notion of the tumor acidic microenvironment benefiting the tumor, gliomas included, is well established, with a number of drugs that could target tumor lactate transporters and pH modifiers [9]. It also seems that the metabolic activities of mutated IDH1/2 enzymes would also play a role in this space, so it is still not clear why these mutated genes/gene products would associate more closely with histologically and functionally lower-grade tumors. On the other hand, the case for metabolic reprogramming of glioma stem cells and its impact on the microenvironmental pH can clearly be made [10], thus at least conceptually linking the de-differentiated tumor status to the genetic phenotypes of the V-ATPases. The molecular connections have yet to be made, but a unifying framework of metabolism, microenvironment, and "stemness" may be in place.

Another point to make concerning the findings of Terrasi et al. is that the V-ATPase content of tumors in relation to tumor grade and outcomes represents a different perspective from our typical signaling-centric views of cancer and how we classify it and treat it. Rather than aberrant kinase/phosphatase activities, we see here how differential expression and utilization of a complex molecular enzyme unit may be linked to features of cancer stemness and aggressiveness. Fundamental

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properties of metabolism, long considered an esoteric niche in the wave of the genomic revolution, are now viewed as important, but complicated, pieces in the puzzle of cancer biology and therapy. V-ATPase research has gone on for decades–studies like this one pave the way for more unbiased approaches to cancer research, and tend to highlight that, indeed, everything old is new again.

## Conflict of interest

The author declares no conflict of interest.

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