Neuron

CellPress

Previews

Glutamate promotes glioma growth via a non-excitable, receptor tyrosine kinase-mediated mechanism

Xi Huang[1,2,3,*] and Michael D. Taylor[1,2,4,5,6,7,8,9,10,11,*]
[1]Developmental, Stem Cell & Cancer Biology Program, The Hospital for Sick Children, Toronto, ON, Canada
[2]Arthur and Sonia Labatt Brain Tumour Research Centre, The Hospital for Sick Children, Toronto, ON, Canada
[3]Department of Molecular Genetics, University of Toronto, Toronto, ON, Canada
[4]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
[5]Department of Surgery, University of Toronto, Toronto, ON, Canada
[6]Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada
[7]Department of Neurosurgery, Texas Children's Hospital, Houston, TX, USA
[8]Texas Children's Cancer and Hematology Center, Houston, TX, USA
[9]Department of Pediatrics - Hematology/Oncology, Baylor College of Medicine, Houston, TX, USA
[10]Department of Neurosurgery, Baylor College of Medicine, Houston, TX, USA
[11]Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX, USA
*Correspondence: xi.huang@sickkids.ca (X.H.), mdt.cns@gmail.com (M.D.T.)
https://doi.org/10.1016/j.neuron.2025.10.007

In this issue, Anastasaki et al.[1] show that glutamate promotes proliferation of pilocytic astrocytoma cells. The authors demonstrate that glutamate receptors activate mitogenic PDGFRα signaling without altering the electrical properties of tumor cells, providing new understanding of how neurotransmitters enhance tumor growth.

Neurons are an integral component of the tumor microenvironment, playing key roles in the life cycle of cancer, including initiation, progression, metastasis, and recurrence (a collection of recent reviews can be found here[2]). Neurotransmitter-mediated neuronal control of tumors is at the center of the cancer neuroscience field. Neurotransmitters, such as glutamate, gamma-aminobutyric acid (GABA), acetylcholine, and dopamine, govern diverse cancer cell behaviors.[2] Neuroactive drugs can mitigate tumor proliferation, invasion, and drug resistance in mice and are being tested as cancer therapies in clinical trials.[2] As the textbooks tells us that neurotransmitters act through modulating the electrical properties of neurons, it may be easy to postulate that neurotransmitters control tumor growth via a similar mechanism. In this issue of *Neuron*, Anastasaki and colleagues demonstrate an exciting, non-excitable mechanism for glutamate to promote the proliferation of tumor cells in the most common pediatric brain tumor, pilocytic astrocytoma (PA).[1]

The authors first analyzed single-cell RNA sequencing (scRNA-seq) datasets of human PA tumors. Interestingly, the top 10 upregulated pathways are related to synapse, dendrites, neuronal spine, and glutamate receptors (GluRs). This finding led the authors to investigate the functional significance of glutamate. Using PA cells lines, including those harboring *KIAA1549:BRAF* rearrangements or biallelic *NF1* loss (two common genetic events in PA), they found that glutamate or compounds that activate N-methyl-D aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), or kainate GluRs increased PA cell proliferation. Considering that cerebellar neurons innervate the brain regions where PAs occur in children, the authors isolated cerebellar neurons from mice and performed neuron-PA cell co-culture or PA cell culture with conditioned medium from the neurons. Both conditions elevated PA cell proliferation. Together, these findings demonstrate that glutamate and neurons induce PA cell proliferation *in vitro*.

Then, the authors performed a series of experiments that led to striking observations. Using three approaches, (1) whole-cell patch clamp recording, (2) multi-electrode arrays, in which microscopic electrodes detect sporadic and coordinated electrical signals of cells, and (3) calcium imaging, the authors found that glutamate did not elicit action potentials or excitatory postsynaptic currents and did not alter the electrical or calcium spike rates of PA cells. These data suggest that glutamate enhances PA cell proliferation through a mechanism not involving modulating their electrical properties.

Next, they set out to determine whether pharmacological inhibition of GluRs can be used to treat PA. After testing multiple GluR antagonists, they identified memantine as the most potent agent in reducing glutamate-induced PA cell proliferation. Oral memantine treatment decreased PA cell proliferation in a patient-derived xenograft (PDX) mouse model. By interrogating RNA sequencing data and tumor tissue microarrays, the authors identified glutamate ionotropic receptor delta type subunit 2 (GRID2) and glutamate ionotropic receptor kainite type subunit 3 (GRIK3) as candidate functional GluR subunits in PA cells. Indeed, genetic knockdown and overexpression decreased and increased PA cell proliferation *in vitro* and *in vivo*, respectively.

The authors further sought to determine the mechanism that underlies the mitogenic function of glutamate. As rat

sarcoma-extracellular signal-regulated kinase (RAS-ERK) signaling drives PA growth, genetic silencing and overexpression of GRID2 or GRIK3 decreased and increased RAS and ERK activation, respectively. Memantine blunted the pro-proliferation effect of glutamate. Further interrogation of the PA scRNA-seq dataset revealed *PDGFRA* expression in tumor cells, suggesting that PDGFRA may be the receptor tyrosine kinase (RTK) upstream of RAS and ERK. In support of this notion, avapritinib, a selective PDGFRα inhibitor that can cross the blood-brain barrier (BBB), reduced glutamate-mediated PA cell proliferation *in vitro* and in PDX. Conversely, PDGFRα overexpression, or treating PA cells with its ligand PDGF-AA, increased ERK activation and PA cell proliferation. Importantly, PDGFRα overexpression following either GRID2 or GRIK3 knockdown had no effect, highlighting that GluR activity is required for PDGFRα signaling to exert its mitogenic effect. Consistent with previous reports that GluR can transactivate RTK through the sarcoma proto-oncogene (Src) kinase, GRID2 or GRIK3 overexpression and genetic silencing induced and reduced Src activation, respectively. Similarly, glutamate activated Src, PDGFRα, and ERK and enhanced PA cell proliferation, whereas these effects were blocked by memantine or the Src inhibitor dasatinib. Lastly, the authors showed that glutamate increased high-grade glioma (HGG) cell proliferation. Similar to PA cells, these phenotypes in HGG cells can be attenuated by memantine, dasatinib, or the PDGFRα inhibitor avapritinib, suggesting that the discoveries in PA may have broader applicability in other glutamate-regulated cancers.

There are three significant contributions from this work. First, a major pillar of cancer neuroscience research is to elucidate how neurotransmitters exert their functions in tumors. Notwithstanding that many studies reported glutamatergic neurons innervate tumors, identified synaptic connections between glutamatergic neurons and tumor cells, and showed that glutamate promotes tumor proliferation, how glutamate exerts its mitogenic function remains poorly understood. While the mechanisms are likely diverse in different cancers, this work demonstrates that glutamate can enhance tumor cell proliferation by activating RTK signaling without invoking changes in membrane potential or calcium signals typically seen in the post-synaptic neuron of a classical glutamatergic synapse. This important advancement would prompt researchers to consider non-electrical consequences when studying the downstream mechanisms of neurotransmitters in cancer.

Second, RTK activation is a frequent event in human cancers, with ∼30% of all RTKs being mutated or overactivated in various cancer types. Amplification, translocation, or mutations in the *PDGFRA* gene can lead to constitutive activation of the PDGFRα signaling pathway. Findings of this work raise the intriguing prospect that glutamate, a widely present neurotransmitter in the tumor microenvironment, determines the signaling output of PDGFRα pathway. While GRID2 and GRIK3 are key GluR subunits in PA, researchers can profile the transcriptomic and proteomic datasets of other cancer types to uncover which GluRs correlate with PDGFRα pathway activation, which could guide future functional experiments.

Third, memantine is a generally well-tolerated drug that has been used to treat Alzheimer's disease and dementia for decades. In addition to inhibiting GluRs in tumor cells, memantine may inhibit NMDA receptor-mediated calcium influx in neurons to mitigate excitotoxicity, a common phenomenon that underlies seizures and neuronal loss in brain tumor. Further, memantine was reported to mitigate cognitive decline in patients with brain metastasis after whole brain radiation therapy.[3] These benefits provide a strong impetus to consider memantine in the treatment of PA.

This study raises several interesting questions for future research. While the authors established cerebellar neurons as a source of glutamate for PA cells, glia cells are an essential regulator of glutamate levels in the brain. In the synaptic cleft, high levels of glutamate are taken up by astrocytes. Astrocytes can then convert glutamate into glutamine and transport it back to neurons for the production of glutamate. This process is known as the glutamate/glutamine cycle. Glial cells themselves can release glutamate to fine-tune the excitability of their neuronal neighbors.[4] Glioma cells can also produce glutamate.[5] Comprehensively mapping the sources, transport mechanisms, and metabolic pathways of glutamate in PA may uncover new therapeutic opportunities.

Ionotropic GluRs comprise four families: AMPA receptors, NMDA receptors, kainate receptors, and δ GluRs. GluRs are assembled by multiple subunits and can permeate sodium, potassium, and calcium. The specific combination of subunits determines their functional properties (ion selectivity, conductance etc.) and pharmacological profiles. While GRID2 (a δ glutamate receptor subunit) and GRIK3 (a kainate receptor subunit) are overexpressed in PA, it would be interesting to identify their interacting GluR subunits, which may not necessarily display altered expression when compared to non-tumoral cells. In normal brain, GRID2 (on the post-synaptic cell) can form a triad complex with cerebellin (a secreted adaptor protein) and neurexin (on the pre-synaptic cell) to regulate synapse properties.[6] Identifying the interacting proteins of GRID2 and GRIK3 and disrupting their protein-protein interactions may provide therapeutic opportunities. Beyond controlling electrical properties, sodium and potassium can regulate intracellular osmolarity to influence molecular crowding. It would be interesting to determine whether sodium and potassium flux through GluRs to modulate macromolecular crowding and signaling (including but not limited to the GluR-Src-PDGFRα-ERK axis) in PA cells. Further, intracellular sodium levels can regulate salt-inducible kinases (SIKs).[7] Potassium can directly bind to cytosolic enzymes, such as pyruvate kinase,[8] to modulate their enzymatic activities or interact with genomic DNA to stabilize its secondary structure such as the *G-quadruplexes* (G4s).[9] It would be interesting to determine whether glutamate modulates intracellular sodium or potassium levels, which in turn regulate these diverse sodium- or potassium-dependent processes in PA cells. In support of this notion, a calcium-impermeable Grid2 mutant can rescue multiple synaptic and motor defects of Grid2 knockout mice, indicative of a calcium-independent role of Grid2.[10]

Neuron-cancer interactions are bi-directional. While this study shows how neurons signal to PA cells, uncovering how PA cells

remodel neuronal activities and the expression, trafficking, and release of neurotransmitters may illuminate new paths to disrupt this reciprocal relationship. Further, it would be interesting to contemplate whether the coupling between glutamate, GluRs, and RTK signaling is operational in other neoplastic cell behaviors (migration, survival, differentiation, etc.), at various cancer stages (initiation, metastasis, recurrence, etc.), and in non-glioma cancer types. Lastly, how many other neurotransmitters, such as GABA and acetylcholine, also exert tumor-modulating functions via non-electrical mechanisms? In sum, this study[1] made important contributions in advancing our understanding of the neuronal control of gliomas and offered ample inspirations for future studies.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Polyserine likes the tau and not the label

Jay P. Ross[1] and Aaron D. Gitler[1,*]
[1]Department of Genetics, Stanford University School of Medicine, Stanford, CA, USA
*Correspondence: agitler@stanford.edu
https://doi.org/10.1016/j.neuron.2025.09.019

Aggregation of the protein tau is a feature of several neurodegenerative diseases. In this issue of *Neuron*, Van Alstyne et al. report a polyserine-motif-based strategy to target aggregation inhibitor proteins to tau aggregates, reducing pathology and rescuing neurodegeneration in animal models.

A classic hallmark of several neurodegenerative diseases is the accumulation of the protein tau into toxic structures in the brain called neurofibrillary tangles. Normally, tau binds to and stabilizes microtubules, which are essential tracks used to transport vesicles and cargo up and down axons. However, in diseases like Alzheimer's, tau becomes hyperphosphorylated, loses its ability to stabilize microtubules, and forms aggregates in the brain. In diverse neurodegenerative disorders where tau is implicated—collectively referred to as tauopathies—tau pathology forms through several different routes, and the sizes and three-dimensional shapes of the filamentous tau inclusions differ in each disease.[1]

Do tau aggregates directly cause disease, or are they instead a downstream consequence of neurodegeneration? Several lines of evidence put tau in the driver's seat. First, mutations in the tau gene that cause a familial form of frontotemporal dementia make tau more prone to aggregation. Second, forcing tau to aggregate in cells is toxic.[2] Third, in Alzheimer's disease, the speed of cognitive decline tracks tightly with the appearance of tau aggregates in the brain. Fourth, and perhaps the most compelling, we have entered a disease-modifying therapy era: a tau-targeting nucleic acid drug is being evaluated in people with Alzheimer's disease and, so far, has shown dramatic reductions in tau pathology in the brain and favorable trends in improving cognition.[3] Now that we know tau aggregation is deleterious and that reducing tau aggregates is beneficial, the next step is to figure out what causes tau to aggregate in the first place, which will help suggest new ways to stop it.

In this issue of *Neuron*, Van Alstyne et al. come up with a clever strategy to selectively target a protein to the existing tau aggregates and reduce tau's ability