



PI3K/AKT/mTOR pathway in tumor progression of oligodendrogliomas

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Glial tumors, also called gliomas, are classified into various subtypes, depending on the cell type from which they originate and the degree of differentiation and malignancy. The most common gliomas are astrocytomas (which originate from astrocytic cells), oligodendrogliomas (OD—from oligodendroglia cells) and ependymomas (from ependymal cells) (1).

Gliomas represent about 80% of primary malignant brain tumors. Low-grade gliomas are more frequent from 20 to 40 years, while the so-called anaplastic or “malignant” gliomas have a generally later onset, from 40 to 70 years. Over the age of 70, glioblastoma (GBM) (grade IV glioma) is the most frequent histological form (2).

Oligodendrogliomas are infiltrating tumors that arise in the white matter of cerebral hemispheres with a better prognosis and sensitivity to treatment than glioblastomas, however as also Tateishi and collaborators mentioned OD often undergoes malignant progression. According to the WHO classification (3) the presence of a 1p/19q codeletion is the main characteristic of OD but different molecular profile may occur (i.e., promoter hypermethylation of the *MGMT* gene, mutations of the *IDH1* or *IDH2* gene) (4). The genetic loss on chromosomes 1p/19q identifies a distinct entity among oligodendrogliomas endowed with a prolonged natural history irrespective of treatment, and higher sensitivity to radio- and chemotherapy (5,6). Oligodendrogliomas are for the 70% low-grade (grade

II), while 30% are anaplastic oligodendrogliomas (AOD) (grade III). The first-line treatment is surgical resection followed by radiotherapy (RT), but adjuvant chemotherapy has been evaluated in clinical trials. In fact, randomized prospective trials have demonstrated that RT followed by procarbazine plus lomustine and vincristine (PCV) chemotherapy improves the overall survival (OS) of these patients compared to RT alone (7). A phase III randomized trial (RTOG 9602) has demonstrated the efficacy of PCV chemotherapy before RT in AOD (8). In 2003, a trial in patients with newly diagnosed low-grade gliomas treated once a day for five days had shown the efficacy of temozolomide (9). Moreover, a randomized phase III trial for patients with newly diagnosed co-deleted 1p/19q anaplastic glioma or high-risk low-grade glioma is currently ongoing. Aim of the study is to determine whether patients treated with RT, associated with concomitant and adjuvant temozolomide, have a better PFS compared to patients who receive RT followed by PCV chemotherapy (NCT00887146).

To date, in ClinicalTrials.gov 252 studies, among recruiting and completed trials, are listed in patients diagnosed with AOD or low grade oligodendroglioma. In particular, different studies are completed or ongoing with the kinase inhibitors dabrafenib or trametinib in patients with BRAF V600 mutated tumors (NCT02684058) or with the EGFR inhibitor erlotinib (NCT01103375). However,

only 6 out 252 studies are carried out in patients with oligodendroglioma using drugs that directly interfere with AKT/PI3K/mTOR pathway.

In fact although PI3K/AKT/mTOR pathway is one of the almost inevitably altered molecular pathways in IDH-wildtype gliomas no clinical benefit were reported in glioma patients treated with drug that inhibit this pathway. Therefore, to date, like in other types of cancer, it has turned out to be challenging to translate the extensive knowledge on PI3K/AKT/mTOR pathway alteration into clinical benefit.

Many *in vitro* and *in vivo* studies report the activation of the PI3K/AKT/mTOR pathway at various levels in brain tumor. This activation does not only concern cancer cells but also cells from the microenvironment (10-12). Recently we showed that in microglia associated to GBM mTOR is activated in about 25% of microglia/macrophages present in the specimens of 42 GBM patients (12). Interestingly Tateishi clearly showed that activation of the PI3K/AKT/mTOR pathway is modified in OD disease; in particular they show that PI3K/AKT/mTOR pathway is an oncogenic driver and is associated with xenograft formation in ODs.

As early as 2005 it was observed that the toxicity profile of mTOR or PI3K inhibitors was unfavorable in brain cancer patient population (13-15). In fact, it would seem that the PI3K/AKT/mTOR pathway is overall too promiscuous, resulting in non-favorable tolerability and safety profiles upon pharmacological inhibition. Moreover, well designed clinical trials have indicated that currently available agents may be insufficient to inhibit the target adequately at doses that are tolerated by patients. Therefore it may possible speculate that even those tumors that are in principle sensitive to target inhibition will rapidly develop escape pathways, circumventing the block of the PI3K/AKT/mTOR pathway (16).

Tateishi and collaborators hypothesized that preclinical models of OD could facilitate identification of therapeutic targets in progressive OD. This hypothesis is applicable to any well-structured preclinical pathology model. Preclinical models guide the clinical experimentation of new drugs and help identify etiopathological mechanisms; this is also true for brain tumor pathologies.

In the project work of Tateishi and colleagues, two anatomically distinct tumor samples from a patient who developed progressive AOD, were collected for orthotopic transplantation in mice. In addition, they implanted 13 tumors to investigate relationship between PI3K/AKT/

mTOR pathway alterations and OD xenograft formation. The published data are absolutely convincing and the authors' discovery adds knowledge about the mechanisms of OD progression. It should necessarily increase the numbers of observations and make a sub-classification based on molecular subtypes to know if and what kind of impact this discovery can have. Therefore, although the observation is important, the limited number of samples limits its conclusions. However, in the panel of OD xenografts of authors, the presence of activating mutations in PI3K/AKT/mTOR pathway was consistently associated with xenograft establishment (6/6, 100%).

In detail the authors show that a specimen from the tumor site that subsequently manifested rapid clinical progression contained a PIK3CA mutation E542K, and yielded propagating xenografts that retained the OD/AOD-defining genomic alterations (IDH1R132H and 1p/19q co-deletion) and PIK3CAE542K, and displayed characteristic sensitivity to alkylating chemotherapeutic agents. In contrast, a xenograft did not engraft from the region that was clinically stable and had wild-type PIK3CA. OD/AOD that failed to generate xenografts did not have activating PI3K/AKT/mTOR alterations (0/9, $P < 0.0001$). Importantly, mutant PIK3CA OD xenografts were vulnerable to PI3K/AKT/mTOR pathway inhibitors *in vitro* and *in vivo*, evidence that mutant PIK3CA is a tumorigenic driver in OD.

Tateishi and collaborators conclude writing that the findings of their research have implications for therapeutic targeting of PI3K/AKT/mTOR pathway activation in progressive ODs. However, although the research of Tateishi and co-workers is well conducted, their conclusions do not take into account the important role that PI3K/AKT/mTOR pathway has in many other districts and physiological role that this pathway conducts. In addition they does not take into account as so far demonstrated (and robustly discussed in this commentary) the blocking of this pathway brings no clinical advantage for the category of patients with brain tumors, among which the gliomas.

Therefore, if on the one hand the value of this research adds important information on the progression of OD on the other could not bring improvements to the patient. Future efforts will have to employ more potent agents or will have to rely on combinatorial strategies, the development of which, however, probably requires a deeper understanding of how the PI3K/AKT/mTOR pathway interacts with other pathways that are likely to be altered in brain tumors.

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.02.72>). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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