



# Diffuse intrinsic pontine gliomas: the future of combination therapy with mTORC1/2 inhibitors and radiation

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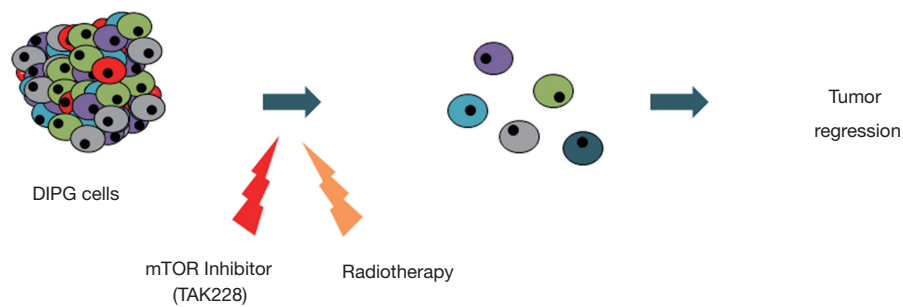
## Diffuse intrinsic pontine gliomas (DIPGs) introduction

DIPGs, even though rare in adults, account for 10 percent of all childhood central nervous system tumors and comprise 75–80% of brainstem tumors in children. While DIPGs are usually diagnosed when children are between the ages of 5 and 9, they can occur at any age in childhood. These tumors are currently the number one cause of brain tumor related death in children, being the median survival only 9 months post-diagnosis and with a survival rate of less than 1% in 5 years (1). DIPGs are highly aggressive and difficult to treat. They diffusely involve the pons and due to the location, the surgical intervention is not a therapeutic option thus currently, palliative radiation therapy is the standard treatment. In the past decades, over 250 clinical trials have been performed using different adjuvant chemotherapy, but there has not been any improvement in patient survival when compared to radiotherapy alone and therefore the treatment has not changed for decades (1). It is urgent to improve current therapies to reduce the mortality rate of this tumor, and the first approach may be to sensitize the tumor to the radiotherapy, making it more effective. Biological information has been missing for a long period of time, since biopsies were considered too risky for the patient's survival and the histopathological analysis did not improve the prognosis or the therapeutic approach. After demonstrating the safety of the stereotactic surgery and together with the samples from the autopsies, a sufficient number of samples have been collected and analyzed to obtain extensive genomic profiling. This has provided

important molecular information on this tumor. Among the different alterations, mutations in Histone 3 (H3K27M), mutations in TP53 and different genomic alterations such as gain of AKT and loss of PTEN have been described (2–4). In fact, the PI3K/AKT/mTOR signaling pathway has been shown to be aberrantly active in 70% of DIPGs (4).

## Function of mTOR signaling pathway in brain tumors

mTOR is a serine/threonine kinase protein that forms two multiprotein complexes, mTORC1 and mTORC2. They differ in the components and in their phosphorylation targets, which cause them to have different cellular functions. mTORC1 stimulates cell proliferation and growth via eIF4E binding proteins and S6 kinases, inhibits autophagy, regulates lipid synthesis and mitochondrial metabolism, as well as the translation process of proteins related to cell growth. mTORC2 controls metabolism, cell survival and cytoskeletal organization via phosphorylation of Akt, SGK1 and PKC (5). These two complexes are also differentially regulated and present different sensitivity to drugs. Furthermore, the mTORC1 activation inhibits mTORC2, a positive regulator of AKT. Since the PI3K/AKT/mTOR signaling pathway regulates cell growth and metabolism it has been extensively analyzed in cancer studies. This pathway is active in different types of cancer, including brain tumors, and it affects the viability and proliferation of several cancer cell lines. Therefore, this pathway has been postulated as a target for alternative treatments (6). In recent years the inhibition of mTOR has



**Figure 1** The work of Miyahara *et al.* (10) shows that mTORC inhibitor TAK228 decreases the activity of mTORC1 and mTORC2 pathways, promoting a reduction of cell growth, suppression of invasion and inhibition of tumor formation in DIPG cells. Moreover, TAK228 enhanced radiotoxicity inducing apoptosis. DIPG, diffuse intrinsic pontine glioma.

been a priority of the research community and numerous inhibitors have been developed, being the best-known rapamycin. Several clinical trials have been performed using rapamycin or an analog (rapalogs) in which they have shown antitumor activity and mild toxicity in patients (6). In addition to an antiproliferative effect, these inhibitors are capable of sensitizing the tumor against standard treatment in brain tumors (7,8). A major limitation of rapamycin and the rapalogs is that they inhibit preferentially mTORC1. Rapamycin is an allosteric inhibitor of mTORC1 while mTORC2 is not susceptible to rapamycin. Since mTORC1 is a negative regulator of mTORC2, this may lead to the upregulation of mTORC2 and AKT, due to a regulatory feedback, mitigating the effect of the drug. This regulatory feedback might be the reason why promising results are lacking when transferring rapamycin and the rapalogs into the clinical practice, particularly in DIPGs (9).

### **mTORC1 and mTORC2 hyperactivation in DIPG and novel therapeutic strategy using mTOR TAK228 Inhibitor**

Considering the above it is clear that an efficient approach to inhibit the mTOR pathway in DIPG is lacking and a recent study conducted by Miyahara and collaborators tried to address this issue (10). One highlight of the study, published in Cancer Letters, was the use of a dual mTORC kinase inhibitor with the same ability to inhibit both mTORC1 and mTORC2 (TAK228) in DIPG cells. With the purpose of evaluating the effectiveness of TAK228 in this type of tumor, they used three primary DIPG cells. They first analyzed the activity of the mTOR pathway and observed a downregulation in the phosphorylation of both S6 at Ser240/244 (substrate of mTORC1) and AKT

at Ser473 (substrate of mTORC2) (10). The inhibition, by TAK228, of the mTOR pathway results in a reduction of cell growth due to a halt in proliferation and an increase in apoptosis. According to that, several studies have shown how a combination therapy can be the most effective therapeutic option in cancer (8). Indeed, in this study, Miyahara *et al.* have shown a cooperative antiproliferative sensitization by TAK228 to radiation therapy. They find a synergistic effect of TAK228 and radiation both in diminishing proliferation and increasing apoptosis (*Figure 1*) (10).

All these results prompted Miyahara and collaborators to investigate the mechanism by which TAK228 was sensitizing the tumor cells to the radiation therapy. They analyzed the expression pattern of two pro-survival factors, BCL-2 and BCL-XL, finding a synergistic decrease of their expression when combining both radiation therapy and TAK228 treatment, in 2 out of 3 cell lines. To further analyze the effect of blocking both mTORC1 and mTORC2 in DIPG cells, the authors investigated the invasion rate of the cells with the TAK228 treatment. They observed a reduction of around 80% as early as 24 hours after the treatment (10). Finally, they assessed the effect of using TAK228 in a murine DIPG cell line. After demonstrating the inhibition of the pathway, they observed a decrease in migration and an increase in apoptosis, similar to the results obtained in human DIPG cells. This encouraged them to analyze the effect of treating mice *in vivo* with TAK228. With this purpose, they injected the murine DIPG cells into the pons of NOD-SCID immunodeficient mice and treated half of the group with TAK228. The results showed a statistically significant increase in the survival of TAK228-treated mice when compared to the survival of control mice (10).

In summary, the present study highlights the need for effective combination therapies to improve the survival rate

of patients with DIPG. Miyahara and collaborators propose TAK228, a dual mTOR kinase inhibitor as a promising therapeutic contender. The inhibition of the PI3K/AKT/mTOR signaling pathway after treatment with TAK228 repressed cell growth, proliferation and invasion while increasing apoptosis in DIPG cells, and extended the life of tumor-bearing mice. The authors have provided evidence that could be sufficient to design a phase I clinical trial in children with DIPG based on their preclinical data.

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