**The Severity of Diffuse Intrinsic Pontine Gliomas (DIPG) and Possible Treatments**

Author: Emily Elving
Major: Microbiology, Cell & Molecular Biology
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

**Key Words:**

Diffuse intrinsic pontine glioma, histones, cell of origin, Hedgehog signaling pathway, CDK7

**Diffuse intrinsic pontine gliomas (DIPG) are aggressive brain tumors that form on the brain stem. They generally come with a very unfortunate prognosis and patients generally have 8-11 months to live. In the last 10 years, research has increased, but the prognosis does not show it. Besides chemotherapy, which has been shown to slightly decrease the size of the tumor, researchers are still searching for better and more effective treatments. DIPG is the most common brain tumor that develops in children and represents 75-80% of pediatric cancers. It is almost universally fatal, impossible to operate on and very difficult to treat. Recent research has showed some promise in finding a possible animal model as well as adding in new strategies for treatments. One of the biggest issues that is run into is the lack of ability to operate on these tumors to allow for any sort of remission. However, research continues to progress, and hope is evident.**

**Introduction**

Diffuse intrinsic pontine gliomas (DIPG) are rare and aggressive tumors that mainly affect children under the age of 15. They form on the brain stem making them difficult to operate on. The survival rate within a year of diagnosis is very low, as is the survival rate after 2- and 5-years post-diagnosis. The median age of children affected with DIPG is 6-7 years of age and they are very rare in adults (Monje et al., 2011). Due to a lack of funds research was limited until about 10 years ago, when it began to pick up. A large focus has been made on ways to treat the tumor that do not involve removing it, because of its location, but finding a suitable animal model has been difficult. Despite over 250 clinical trials, “no drugs have shown efficacy in this malignancy” (Phillips et al., 2019). Research has been generated about the possibility of the Hedgehog signaling pathway being studied in mouse models. There has also been a lack of available tumor tissue. Methods to discover the cause of DIPG have also been researched, but brain tumors are difficult to figure out regardless. Many signaling pathways and histone mutations have been considered culprits, however, with these discoveries comes the unfortunate lack of ability to isolate and identify them as issues in the first place. So, as far as research has come in the past decade, many roadblocks still lie in the way of guaranteeing new treatment methods that will affect the growth of DIPG.

**Recent Progress**

When dealing with diseases and infections, one of the most important factors of research is the ability to identify causes and link them to certain characteristics of said disease. With DIPG, this factor is one of the biggest roadblocks. Finding connections between DIPG cases in terms of what is uncovered between certain tumors is a fantastic way to build up research on them. However, experiments on these detections are almost impossible without an animal model to focus the experiments on. In a 2011 study, it was found that “the Hedgehog (Hh) signaling pathway implicated in many developmental and oncogenic processes is active in DIPG tumor cells” (Monje et al., 2011). The Hedgehog (Hh) signaling pathway is a pathway that regulates the survival and proliferation of tissue and stem cells (Briscoe et al., 2013). It’s function also gives rise to tumor formation. Modulating the Hh pathway has been shown to have consequences on DIPG self-renewal. Using mouse models, Michelle Monje, along with other scientists, were able to discover a pontine precursor-like cell (PPC) population that is “temporally and anatomically restricted to the time and place that DIPGs form” (Monje et al., 2011).

The PPC population is also immunophenotypically similar to DIPG. The results also show that if the Hh signaling pathway is unregulated in the murine counterpart of the PPC population, ventral pontine hyperplasia occurs, suggesting that the cells may be susceptible to transformation. With these factors in mind, the conclusion arose that this cell is a candidate for the cell of origin for DIPGs and ideas for unique therapeutic treatments for DIPG could come from this research.

Besides finding an animal model, it is important to continue to consider the danger in operating on DIPGs. Their location on the ventral pons poses a high risk of death if operated on, and even biopsies of this tumor are very rare. In most cases, DIPG has only been treated with the use of radiation and chemotherapy, but the aggressiveness of the tumor renders these treatments ineffective. Luckily, in recent years, research has progressed.

In a 2017 study done by Surya Nagaraja and a team of other scientists, they focused on methods of disrupting transcription. Their experiment followed the previous discoveries that a histone-3 K27M (H3K27M) mutation affects about 80% of DIPG cases. In 2014, Oren J. Beecher and Robert J. Wechsler-Reya examined this histone mutation. The mutation causes lysine 27 to change to methionine which then leads to the inhibition of Polycomb repressive complex 2 (PRC2). This inhibition results in normally repressed loci becoming activated. The H3K27M mutation combined with a lack of the TP53 tumor suppressor create the rise to gliomas in mouse models (Becher & Wechsler-Reya, 2014). In Nagaraja’s experiment, the evidence of aberrant transcription caused by the H3K27M mutation was used to hypothesize that a possible blockage of this transcription as a whole could affect DIPGs. The experiment showed the vulnerability DIPG has that is caused by the inhibition of transcription. One big discovery was the use of a cyclin-dependent kinase 7 (CDK7) blockade to disrupt transcription. Nagaraja used THZ1, a highly specific CDK7 inhibitor, to create the CDK1 blockade. THZ1 has been used in preclinical models for many other malignancies to inhibit CDK7. It was found that THZ1 use heavily reduced DIPG cell viability. The results also show that DIPG is “vulnerable to disruption of transcription both in vitro and in vivo” and the use of THZ1 “impairs DIPG cell viability” (Nagaraja et al., 2017). Histone deacetylase (HDAC) inhibitors have also been shown to be effective against DIPG cell cultures and the combination of HDAC with THZ1 has proved to be more effective than inducing cell apoptosis. Patient-derived xenograft models have a modest increase in survival with THZ1 therapy, demonstrating that transcription disruption may have a significant effect on DIPG patients and could be used as a form of treatment when combined with an HDAC inhibitor and drugs created to allow for brain penetration.

**Discussion**

To begin with, after doing a sufficient amount of research, the results of the experiments are valid. In all recent studies done over DIPG, each article seems to have a lot of aspects in common in terms of the discoveries that have been made. Each aspect of research has just been expanded over the years as research on this cancer progresses. The most common topics in almost every paper were about the H3K27M mutation, the lack of the TP53 tumor suppressor, PRC2 inhibition and CDK7 inhibition. The more scientists are able to learn about these tumors, the greater chance there is that a cure can be found. Research is going in the right direction, and there is so much more that can be learned about this fatal tumor.

The results that have been found mainly address new ways in which we could treat DIPGs. The location of the tumors’ growth means that the idea of simply removing the tumor in hopes that remission can be reached is farfetched. There is a small number of DIPG tissue available to study and finding an animal model was very difficult. So, scientists had to dive into the molecular components of the tumor and find things that DIPGs have in common and go from there. The experiment results that show possible avenues for treatments are very promising. The results also show that there are many ways that research could continue to go from here. With the connections found between tumors in each case, scientists will continue to be able to look at current research and develop hypotheses that lead to more possible treatments. New methods in working with animal models have also been addressed; this has always been a large problem with DIPG research. Progression in research has allowed for the discovery of similarities between DIPG and other tumors that develop in mice, meaning scientists can focus their work in mice models. In xenograft models, it has been shown that inhibition methods that scientists focused on were able to increase the rate of survival of the models. Considering the current rate of survival for patients, this is miraculous.

Many questions still remain unanswered with these experiments, although they offer so much. This is fresh research that has come out within the past 5 years; new discoveries may change the results and there is still a lot of information that is unknown. Taking Monje’s experiment for example, the results only offer a candidate for a cell of origin. The possibility exists that there are other cells that could be candidates, and this possibility means years of more testing and experimenting. Also, all of these experiments were done on mouse or xenograft models so, how long is it going to take for clinical trials in humans to begin? Though it is dangerous to operate on DIPGs, in the future, is there a method that could be developed to allow for safe biopsies to start research on growing tumors? There is so much to take into consideration with the evidence already found and the evidence that many hope will be found, and it is going to take a while for scientists to receive the answers that they want.

**References**

Becher, O. J., & Wechsler-Reya, R. J. (2014). For pediatric glioma, leave no histone unturned: Examining histone mutations points to possible therapies for a lethal brain tumor. *Science*, *346*(6216), 1458–1459.

Briscoe, J., & Thérond, P. P. (2013). The mechanisms of hedgehog signaling and its roles in development and disease. *Nature Reviews Molecular Cell Biology*, *14*(7), 416–429. https://doi.org/10.1038/nrm3598

Monje, M., Mitra, S. S., Freret, M. E., Raveh, T. B., Kim, J., Masek, M., Attema, J. L., Li, G., Haddix, T., Edwards, M. S. B., Fisher, P. G., Weissman, I. L., Rowitch, D. H., Vogel, H., Wong, A. J., & Beachy, P. A. (2011). Hedgehog-responsive candidate cell of origin for diffuse intrinsic pontine glioma. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(11).

Nagaraja, S., Vitanza, N. A., Woo, P. J., Taylor, K. R., Liu, F., Zhang, L., Li, M., Meng, W., Ponnuswami, A., Sun, W., Ma, J., Hulleman, E., Swigut, T., Wysocka, J., Tang, Y., & Monje, M. (2017). Transcriptional dependencies in diffuse intrinsic pontine glioma. *Cancer Cell*, *31*(5), 635–652.

Phillips, R. E., Yang, Y., Smith, R. C., Thompson, B. M., Yamasaki, T., Soto-Feliciano, Y. M., Funato, K., Liang, Y., Garcia-Bermudez, J., Wang, X., Garcia, B. A., Yamasaki, K., McDonald, J. G., Birsoy, K., Tabar, V., & Allis, C. D. (2019). Target identification reveals lanosterol synthase as a vulnerability in glioma. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(16), 7957–7962.