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A new era for children with diffuse intrinsic pontine glioma: hope for cure?

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“...diffuse intrinsic pontine gliomas seem to be genetically more closely related to gliomas arising in the thalamus, suggesting a shared origin of a common precursor cell population.”

Diffuse intrinsic pontine gliomas (DIPGs) are devastating tumors that almost exclusively occur in children. They comprise 7–8% of all pediatric CNS tumors and are the most frequent of all malignant gliomas in children [1]. Over the past 30 years, the prognosis has remained equally dismal, with <10% of the patients being alive 2 years from diagnosis [2,3]. A major problem in the treatment of DIPG is its delicate location and diffuse spread in the pons, meaning that radical surgical resection is not an option. Radiotherapy is a standard treatment for DIPG, often showing tumor reduction and clinical improvement, although these effects are always temporary [4]. Hyperfractionated radiotherapy, combination chemotherapy and unselected single-agent targeted therapy trials have not improved the prognosis thus far [2,3].

“The availability of tumor tissue has initiated a real catch-up in the exploration of diffuse intrinsic pontine glioma biology over the past 2 years.”

However, over the past few years, the knowledge on DIPG has increased considerably. This is due to the recent availability of tumor material as a result of reintroduced biopsies and autopsies. For a long time, biopsies were considered as a dangerous but also unnecessary procedure, since MRI was conclusive for diagnosis, and the histology would not alter therapies [5]. But times are changing, and many groups

have started taking biopsies again [6,7]. A group in Paris stereotactically biopsied over 100 patients, reporting 0% mortality and 4% transient morbidity [PUGETS, PERS. COMM.]. In addition, postmortem tissue collection was introduced in Canada, the USA and The Netherlands, to address the lack of tumor material for research [8,9]. Biopsy has the advantage of providing non-pretreated material with the presence of original molecular characteristics, while tissue obtained by autopsy has the risk of treatment-related genetic changes. On the other hand, postmortem tissue collection has the benefit of providing much larger amounts of tissue, enabling analysis on the heterogeneity of the tumor [10], and also provides genetic information on the treatment-resistant subclones present at end-stage disease. Moreover, it enables the collection of normal brain tissue of the patient.

The availability of tumor tissue has initiated a real catch-up in the exploration of DIPG biology over the past 2 years. Importantly, studies show a clearly distinct genetic profile of pediatric high-grade glioma (HGG) including DIPG as compared with adult HGG [11]. Moreover, DIPG differs from pediatric HGG occurring elsewhere in the brain, since several chromosomal abnormalities appear more frequently in DIPG than in pediatric HGG, including gains of chromosomes 1q, 2p, 7p, 8q and 9q and losses in chromosomes 10q, 16q and 17p [10,12–15]. Interestingly, DIPGs seem to be genetically more closely related to gliomas

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arising in the thalamus, suggesting a shared origin of a common precursor cell population [13].

At the gene expression level, DIPG is mainly characterized by high PDGF receptor (*PDGFR*) amplification. Other amplified genes in DIPG are hepatocyte growth factor receptor (*MET*), IGF receptor 1 (*IGF1R*), EGF receptors (*EGFR*, *ERBB4* and *EGFRv3*), poly-ADP-ribose polymerase (*PARP*), *VEGFA* and the associated downstream pathways including *PI3K-Akt*-phosphomammalian target of rapamycin (*MTOR*) and retinoblastoma-associated protein (*RB*) pathway [10,12–15]. Puget *et al.* performed comparative genomic hybridization and gene expression profiling on 23 biopsy samples and identified two subgroups; the first characterized by oligodendroglial features appearing largely driven by *PDGFR* and the second by mesenchymal and angiogenesis characteristics showing overexpression of numerous proangiogenic genes including *VEGFA* [13]. The oligodendroglial-like subgroup showed a significantly worse prognosis than the mesenchymal group. These distinct molecular subgroups may benefit from different targeted treatment strategies.

“From the few existing diffuse intrinsic pontine glioma cell cultures, only two have groups reported the development of xenografts thus far.”

Recently, results of the first whole-genome sequencing of seven DIPG samples were reported [16]. One of the main findings was mutations in histone H3 located on chromosome 1. This finding was confirmed by targeted gene sequencing in 43 DIPG samples. Since histone 3 is known to activate multiple genes involved in the rhombencephalon (pons, cerebellum and mesencephalon) development, mutations in histone H3 may drive the development of DIPG as a result of aberrant embryological development. This hypothesis was supported by the fact that these mutations were not found in exome-sequencing data from adult gliomas [16]. Another group suggested that the Hedgehog signaling pathway, which is highly active in DIPG, could be involved in the origin of DIPG [17]. They observed that unregulated activity of the Hedgehog pathway resulted in hypertrophy of the healthy pons of mice [17]. All these exciting new biological insights and discoveries of multiple pathways are helping to increase the understanding of DIPG and developing new multi-targeted therapy approaches for this disease. They will mark the end of an era of unselected single-agent trials based on adult data.

However, with the avalanche of gene profiling studies, two other key issues on the way to better treatment strategies for DIPG remain behind. The first issue is drug delivery: why are all chemotherapy regimens ineffective in DIPG while some show activity in supratentorially located gliomas, such as temozolomide [18]? And why does imatinib, an inhibitor of the DIPG key target PDGFRA, not improve survival [19]? Could poor drug distribution be at least partly the answer to these questions?

Indeed, drug delivery does seem to be a major issue. Penetration of drugs is limited in all CNS tumors but DIPG seems to top all of

them. In contrast to gliomas elsewhere in the brain, DIPGs often show no contrast enhancement on MRI after gadolinium administration [20]. These MRI findings suggest an intact blood–brain barrier (BBB) in DIPG. In the autopsy study the authors have been performing in The Netherlands, the BBB component glutamate was present in all postmortem samples studied so far, which also supports an intact BBB in DIPG [21]. In addition, like in most cancers, drug penetration may be further hindered by drug efflux pumps such as ATP-binding cassette (ABC) B1, ABCC1 and ABCG2, but studies in DIPG are lacking.

To investigate drug distribution and drug resistance in DIPG, *in vitro* and *in vivo* models are essential. This addresses the second key issue; preclinical models for DIPG are still very rare. To date, only two groups have published on DIPG *in vitro* models [17,22]. With the lack of DIPG cell lines, *in vivo* models have been developed using adult glioma cell lines, but these lack the DIPG genotype. Moreover, only few animal models show the diffuse growth typical for DIPG [21]. From the few existing DIPG cell cultures, only two groups have reported the development of xenografts thus far [17,22].

In the future, it is crucial that drug distribution is studied as part of clinical trials. Otherwise, potential drugs will be regarded as ineffective, while they are in fact being inadequately delivered to the tumor. Studying drug distribution is possible by labeling drugs, including specific antibodies and tyrosine kinase inhibitors, in combination with PET imaging and recently also MRI. Multiple immuno-PET studies in adults have proven the value and reliability of this technique [23]. Drug targets were visualized clearly and drug distribution could be analyzed precisely. In children, these studies have not yet been accomplished. Recently, the authors initiated a PET drug-labeling study in DIPG patients using positron emitter zirconium-89 with the aim to non-invasively study target expression, drug distribution and dosimetry. These studies will help to select the right drug for the right patient and/or may encourage finding new routes of administration for potentially effective but poorly delivered drugs.

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Only a few trials have focused on improving drug delivery in DIPG. Intra-arterial infusion of mannitol with concurrent chemotherapy seemed to improve survival. However, this was a retrospective study in children and adults with brainstem glioma including a case presenting with an exceptionally long duration of symptoms before diagnosis, suggesting a more benign tumor of the brainstem. Therefore, selection bias cannot be excluded, and a prospective study in a more strictly defined DIPG population is needed to confirm these results [24]. Opening the BBB by bradykinin to enhance carboplatin distribution did not improve outcome [25]. Recently, the use of

convection-enhanced delivery (CED) was reported in DIPG, a method in which drugs are infused under a continuous pressure gradient for a duration of usually 72–96 h, allowing high local drug concentrations [26,27]. Two children with progressive DIPG were treated with CED, respectively, with IL-13 bounded to pseudomonas exotoxin and nimustine, and in both patients, the toxicity consisted of transient worsening of pre-existing neurological symptoms [26,27]. MRI at 1 month after procedure showed stable disease and partial response, respectively. As of now, two CED trials are open for children with DIPG in the USA, one with IL-13 pseudomonas exotoxin and another with the radioactive iodine-labeled monoclonal antibody 124I-8H9 [101]. These BBB circumventing approaches seem promising and even more strategies can be expected in the near future, including nanoparticles. To test new routes of administration and select the most potential drugs for clinical trials, again, adequate *in vivo* models are crucial. When preclinical results are translated to the clinic, national and international collaborative clinical trials are required, in view of the rarity of the disease.

Conclusion

A new era for DIPG has just begun. Biological insights have increased enormously over the past 2 years. Preclinical DIPG models are still urgently needed to test new treatment strategies resulting from these biological insights. Adequate delivery of drugs is a major concern and should be ensured by distribution studies or, when delivery is failing, by new routes of administration. Eventually, these steps may improve the dismal prognosis of children with DIPG.

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