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Diffuse intrinsic pontine glioma: molecular landscape and emerging therapeutic targets

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Abstract

Purpose of review—Diffuse intrinsic pontine glioma (DIPG) is a fatal childhood brainstem malignancy. Despite advances in understanding of the molecular underpinnings of the tumor in the past decade, the dismal prognosis of DIPG has thus far remained unchanged. This review seeks to highlight promising therapeutic targets within three arenas: DIPG cell-intrinsic vulnerabilities, immunotherapeutic approaches to tumor clearance, and microenvironmental dependencies that promote tumor growth.

Recent findings—Promising therapeutic strategies from recent studies include epigenetic modifying agents such as histone deacetylase inhibitors, bromodomain and extra-terminal motif (BET) protein inhibitors, and CDK7 inhibitors. Tumor-specific immunotherapies are emerging. Key interactions between DIPG and normal brain cells are coming to light, and targeting critical microenvironmental mechanisms driving DIPG growth in the developing childhood brain represents a new direction for therapy.

Summary—Several DIPG treatment strategies are being evaluated in early clinical trials. Ultimately, we suspect that a multifaceted therapeutic approach utilizing cell-intrinsic, microenvironmental, and immunotherapeutic targets will be necessary for eradicating DIPG.

Keywords

diffuse intrinsic pontine glioma; epigenetics; H3K27M; immunotherapy; microenvironment

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

Diffuse intrinsic pontine glioma (DIPG) is a devastating childhood brainstem tumor and a leading cause of pediatric brain tumor-related death. The median survival of DIPG is 9–11 months with a 99% 5-year mortality [1,2,3■■]. DIPG is classified as a subtype of diffuse midline glioma, differentiated by its origin in the pons. The tumor's dismal prognosis arises in part due to this origination in the brainstem where many critical nervous system functions such as respiration are regulated, thus rendering surgical tumor resection impossible. In addition, DIPG diffusely infiltrates pontine tissue and often invades into more distant brain regions [4,5■]. DIPG resistance to conventional chemotherapeutic agents used for brain tumors, such as temozolomide, has added to the challenge of even moderately effective treatment [6,7]. Radiotherapy is presently the sole treatment that has demonstrated clinical efficacy in prolonging life, conferring an average of 3 months survival benefit; the median survival is only 6 months without standard radio-therapy. DIPG still remains universally fatal.

In the past decade, studies of tumor biopsy and autopsy samples have vastly increased our understanding of DIPG's underlying molecular pathogenesis [8]. Eighty-percent of DIPG tumors and a high percentage of gliomas in other midline structures such as thalamus and spinal cord were found to harbor lysine-to-methionine substitutions (K27M) in genes encoding histone H3 [9–11] - these findings mark the first known associations between histone mutations and cancer. The findings that histone mutations delineated a tumor subgroup with unique pathophysiology and prognosis led to the reclassification of H3K27M-mutated DIPG in the 2016 WHO classification of tumors of the central nervous system as diffuse midline glioma with K27M mutation, a shift from the previous anatomical and histological classifications [12]. The H3K27M histone mutation results in dysfunction of the polycomb repressive complex-2 (PRC2) methyltransferase complex and global hypomethylation of the lysine at position 27 of the H3 protein (H3K27), with consequent dysregulation of gene expression [11,13–15]. In DIPG, this broad disruption of epigenetic regulation fosters oncogenesis, in some cases with secondary associated mutations in classical oncogenic pathways [13,16–18]. Recent advances from patient-derived DIPG cell cultures and orthotopic xenograft models have identified promising drug targets that are being investigated further in ongoing preclinical and clinical trials [19,20■]. However, the complexity of DIPG molecular pathogenesis and resistance to conventional therapeutics highlights the necessity of multipronged approaches to DIPG treatment to improve outcomes. Here, we discuss a triad of emerging therapeutic strategies - targeting cell intrinsic vulnerabilities, immunotherapy targeting tumor-specific antigens, and targeting glioma-promoting interactions in the brain microenvironment - and hypothesize that exploiting DIPG vulnerabilities in all three arenas will be necessary to eradicate this devastating tumor.

DEVELOPMENTAL ORIGINS

DIPG arises in a specific spatio-temporal pattern, typically during middle childhood, suggesting tumor cells arise from dysregulation of a normal neurodevelopmental process. Thus, the formation of DIPG is likely dependent on both a susceptible cell of origin and

microenvironmental signaling that promotes or enables tumor formation. The histological findings of enrichment of an early oligodendroglial precursor cell at the age and location of DIPG origination (ventral pons) first suggested that the tumor may arise from precursor cells in the oligodendroglial lineage [21], cells that are engaged in myelin development throughout childhood and adolescence. Recent transcriptional and chromatin landscape studies demonstrate that oligodendroglial lineage genes are activated at both the epigenetic and transcriptional levels in DIPG [20■■,22,23]. In addition, DIPG single cell sequencing studies reveal that the proliferative stem-like cells of primary DIPG tumors closely resemble oligodendroglial precursors; this oligodendrocyte precursor cell (OPC)-like, self-renewing population of malignant cells represents the tumor-initiating cell (or 'cancer stem cell') population in DIPG [24■■]. Several excellent studies have examined the effect of H3K27M mutations in potentiating malignant growth in precursor cells [17,25■,26,27], and clarified differences in DNA methylation and clinical phenotype between H3.1K27M and H3.3K27M DIPG [28–30]. H3.1 K27M tumors originate exclusively in pons, whereas H3.3 K27M mutations give rise to pontine tumors in the case of DIPG, as well as other diffuse midline tumors such as thalamic or spinal cord high-grade gliomas (HGGs) [31,32] - future studies will elaborate on the significance of these anatomical and epigenetic profiles with regards to the origin or treatment of DIPG.

CELL-INTRINSIC VULNERABILITIES

The discovery of heterozygous, clonal K27M histone mutations found in the majority of DIPG tumors has led to a greater understanding of the underlying transcriptional dysfunction that potentiates tumor growth [33,34]. The vast majority of these mutations arise in the histone genes *H3F3A* or *HIST1H3B* encoding the H3.3 or H3.1 variants, respectively [9–11,13,14,16,18,35]. Both H3K27M mutation variants result in global reduction of repressive lysine 27 trimethylation (H3K27me3), resulting in aberrant transcription central to DIPG oncogenesis [13–17]. Initial studies revealed that interaction between the H3K27M oncohistone and the enhancer of zeste homologue-2 (EZH2) component of the H3K27 methyltransferase complex, polycomb repressive complex 2 (PRC2), leads to global hypomethylation of K27 in wild type H3 histones in the cell [11,13,14]. Dysfunction in PRC2 activity is seen even after the methyltransferase complex has dissociated from H3K27M oncohistones [36■,37■■,38], with the loss of methylation leading to subsequent oncogenic gene activation in the glioma cells [11,13,14,36■] (Fig. 1). Therefore, epigenetic modifying therapies which restore normal patterns of trimethylation may be a promising class of agents for DIPG.

Significantly, some genomic areas in H3K27M-mutant DIPG cells exhibit paradoxically increased methylation. Although the H3K27M oncohistone results in dose-dependent inhibition of PRC2 function, strong PRC2 targets (with high concentrations of H3K27me3, CpG islands, or low levels of H3.3K27M as seen in one study) are able to maintain recruitment of PRC2 [37■■,39,40■]. This repressive gene silencing also plays a role in DIPG development, and should be accounted for in future therapeutics.

Histone deacetylase and demethylase inhibitors (Panobinostat)

Inhibitors of histone deacetylases (HDAC) are effective against HGGs and other pediatric central nervous tumors [41,42], and a DIPG drug screen of small molecules found robust anti-DIPG activity of the HDAC inhibitor panobinostat *in vitro* [19]. Histone acetyltransferases lead to lysine acetylation, most frequently on N-terminal tails - in the case of DIPG, it has been speculated that acetylation may disrupt interactions between H3K27M and PRC2 and thus normalize the chromatin environment [43]. Panobinostat was found to increase global H3 acetylation in a dose-dependent manner and partially rescue the H3K27 hypo-trimethylation phenotype. DIPG cells exposed to panobinostat also had lower expression of proliferation associated genes (e.g., *MYC* oncogene), decreased cell proliferation and increased cell death, and DIPG xenografted mice treated with panobinostat exhibited prolonged survival [19]. Another study showed a modest benefit of panobinostat in a murine DIPG model measured by reduced tumor cell proliferation [44]. In a more recent study, panobinostat treatment was found to lead to increased expression of endogenous retroviral elements, possibly providing an alternative mechanism for DIPG sensitivity to HDAC inhibition [45■].

With demonstration of preclinical benefit, panobinostat was moved into clinical trials. A current Phase I trial is testing side effects and optimal dosage of panobinostat in children with DIPG (NCT02717455). Preliminary results reported in abstract form have been encouraging, but it is early to draw conclusions. Although a promising treatment, the current challenges of panobinostat treatment for DIPG is the demonstrated evolution of resistance shown in preclinical studies [19] and limited but present brain penetration of drug. As is a challenge for many DIPG treatments, the intact blood brain barrier surrounding the tumor can make drug delivery challenging, and alternative delivery strategies such as direct intratumoral delivery by convection enhanced delivery are in development (NCT03566199) [46–48]. Combination therapies with panobinostat are promising, including reports of clinical benefit when panobinostat was used in conjunction with reirradiation in DIPG [49].

H3K27 demethylase inhibitor (GSKJ4)

In addition to inhibiting the loss of acetylation to normalize transcription, another strategy to address impaired H3K27 trimethylation in the context of H3K27M-induced PRC2 dysfunction is to stabilize the trimethyl mark on wild type H3K27. GSKJ4, which inhibits the K27 demethylase JMJD3, stabilizes H3K27 methylation in tumor cells and demonstrates antitumor activity [50]. However, inhibition of DIPG growth using this tool compound was seen at concentrations not attainable in clinical settings [19].

Enhancer of zeste homologue-2 inhibitors

In specific cases where tumor suppressor genes such as *p16* are intact, the paradoxical increase in trimethylation and subsequent gene silencing described above promotes tumor growth [26,51]. H3K27M-expressing DIPG cell lines were found to require PRC2 methylation for proliferation and small-molecule EZH2 inhibitors arrest cell growth by increasing transcription of the tumor-suppressor protein p16INK4A normally silenced by PRC2 [26,40■]. However, while no significant cytotoxic impact of EZH2 inhibition by Tazemetostat (EPZ-6438) was found in pediatric GBM/DIPG cells with H3.3 mutations -

this therapy may yet prove effective in combination with other cytotoxic epigenetic modulating drugs [52].

Transcriptional regulation

Given the central role of transcriptional dysregulation in DIPG, an additional strategy has been to directly target efficient transcription by RNA polymerase II complex. Targeting of activating bromodomain proteins with JQ1 has been effective in preclinical models, with BRD4 inhibition shown to disrupt aberrant transcription in DIPG [20■■,36■]. Furthermore, phosphorylation of the C-terminal tail of RNA pol II is required for transcription initiation and CDK7 blockade with THZ1 has importantly shown therapeutic efficacy in DIPG cells resistant to HDAC inhibitor therapy [20■■] (Fig. 1). Combining treatments of epigenetic and transcriptional disruption demonstrates a synergistic effect in disrupting DIPG cell viability [20■■,53]. Although the epigenetic targets highlighted above have shown promising preclinical efficacy, the therapies are by nature nonspecific, and may have effects on other cells types. Targeting pathways that are specific to DIPG may be another important avenue to contain tumor growth and spread.

Secondary genetic alterations

Although several human DIPG tumors are found only to exhibit the histone mutation, H3K27M is not sufficient to induce tumor formation in DIPG models and promotes tumor growth only in combination with mutant p53 and activated platelet-derived growth factor receptor α in experimental settings explored thus far [17,25■,54–56]. In addition, the H3.1K27M and H3.3K27M DIPG subgroups are characteristically associated with differing cooperating genetic alterations [3■■,11,18,35,57]. H3.3K27M tumors associate with mutations in TP53 while H3.1K27M tumors often harbor mutations in *ACVR1* or have PI3K pathway dysfunction [18,25■,28–30,58]. A meta-analysis of over 1000 pediatric high -grade glioma and DIPG cases demonstrated multiple altered pathways previously unrecognized in subsets of tumors such as miRNA regulation, wingless-related integration site (Wnt) pathway and splicing machinery [3■■]. Other subclonal alterations occasionally found in H3.1 K27M DIPGs include PIK3CA mutation, phosphatase and tensin homolog (PTEN) loss, PPM1D mutation, and amplification of cell cycle genes including *CCND1*, *CDK4*, and *CDK6* [59,60].

Several studies have investigated targeting of these biologically relevant pathways in DIPG. For example, the majority of DIPG tumors exhibit dysfunction in PI3K/Ak strain transforming (AKT)/mammalian target of rapamycin (mTOR) signaling pathway [61,62], and dual mTOR inhibitors have shown preclinical efficacy *in vitro* [20■■,63] as well as in a xenograft model [64]. mTOR inhibitors have also shown synergistic effects with CDK4/6 inhibitors which prevent cell cycle progression as well as with mitrochondrial inhibitors although efficacy has been limited in orthotopic xenograft models and in clinical settings, likely due to tumor heterogeneity and poor blood brain barrier penetrance [65,66]. With regard to targeting P53, one study has shown that the inhibition of mutant PPM1D enhances DNA damage response and growth suppressive effects of ionizing radiation in DIPG [67]. Recent studies have additionally demonstrated the ability of ALK2 inhibitors to cross the blood-brain barrier and produced modest preclinical efficacy in *ACVR1* mutant DIPGs as a

single treatment [58,68]. Due to the subclonal nature of secondary mutations, targeted monotherapies will not likely be curative on their own; however, a combinatorial strategy targeting several pathways alongside other treatments may be a necessity to eliminate these heterogeneous tumors.

IMMUNOTHERAPY

Harnessing the host immune response has been critical in improving the outcomes of several malignancies in the past decade. However, the immunosuppressive microenvironment of DIPG may present a challenge for therapeutics that rely on endogenous immune responses. Below we outline recent studies that utilize immunotherapeutic targets in DIPG.

Peptide vaccines

A recent peptide vaccine induces mutation-specific, cytotoxic T-cell-mediated and Th1-cell-mediated immune responses in a mouse model (H3K27M presented on major histocompatibility complex class II) [69]. Another study using autologous dendritic cell vaccines demonstrated that this therapy was safe and generated a DIPG-specific immune response [70]. In contrast to other brain tumors in which peptide vaccines are under investigation, there is very minimal immune infiltration in DIPG. DIPG cells and DIPG-associated macrophages express fewer cytokines and chemokines than in adult glioblastoma [71,72]. This may represent a substantial obstacle to the efficacy of vaccine-mediated strategies, as the lack of lymphocytes and non-inflammatory phenotype of DIPG-associated microglia/macrophages may indicate minimal ability for peptide vaccination to stimulate sufficient endogenous lymphocyte expansion and migration to the tumor site.

Adoptive T-cell therapies

Adoptive T-cell therapies have recently emerged as an extremely promising approach particularly for hematological malignancies [73,74], and a case report in glioblastoma suggests that engineered T cells have the potential to achieve a profound, albeit temporary, response even in advanced stages of disease [75]. Due to their overwhelming prevalence in DIPG, tumor-specific H3K27M peptides represent a target of great interest for engineered T cell receptor (TCR) development. A recent study has demonstrated that the creation of H3.3K27M-specific TCRs was able to kill human leukocyte antigen-$A2^{+}H3.3K27M^{+}$glioma cells and suppress the progression of glioma xenografts in mice [76]. These studies show promise for developing safe and effective T-cell-based immunotherapeutic strategies.

Chimeric antigen receptors (CARs) represent another approach to adoptive T-cell therapies, and recent work identified extremely high expression of the disialoganglioside GD2 in patient-derived DIPG cultures [77■■]. Anti-GD2 CAR T cells incorporating the 4–1BBz costimulatory domain caused antigen-specific cytotoxicity to DIPG cells [78] (Fig. 1). Patient-derived H3-K27M+ diffuse midline glioma orthotopic xenograft models showed near-complete tumor clearance and substantially improved survival after peripheral administration of GD2-targeted CAR T cells [77■■]. Although the majority of mice tolerated the treatment well, the on-target, on-tumor inflammation causes pontine tissue expansion that can compress the fourth ventricle and result in life-threatening hydrocephalus

[77■■]. GD2-targeted CAR T-cell therapy, including the same GD2-directed CAR T-cell construct used in this DIPG preclinical study, has been employed in clinical trials for neuroblastoma (NCT00085930, NCT01822652) and has thus far been well tolerated [79–81]. However, as the brainstem is a precarious neuroanatomical site for swelling, peritumoral edema will be intensively monitored and managed in planned GD2-targeted CAR T-cell therapy clinical trials.

Checkpoint inhibitors

As noted above, the DIPG tumor microenvironment is ‘immune cold’ with minimal programmed death-ligand 1 (PD-L1) expression. A retrospective cohort analysis of children with DIPG who received reirradiation with concomitant programmed cell death protein 1 (PD-1) inhibitor nivolumab demonstrated tolerability and slightly prolonged overall survival (OS) [82]. However, PD-1 inhibitor therapy alone is unlikely to have a robust effect in DIPG and may need to be combined with an additional intervention to enhance the endogenous immune response [71,72].

Immunomodulatory antibodies

Immune modulating monoclonal antibodies are an emerging treatment for a variety of cancers. One such immune modulating antibody, MDV9300 (pidilizumab), has shown efficacy in various pediatric cancers, including hematological malignancies, and was thus tried in DIPG [83]. Pidilizumab is immune modulating humanized IgG1 mAb with secondary inhibitory effects on PD-1, and thus enhances endogenous antitumor immune responses. In a recent clinical trial with 9 patients (NCT 01952769), median event free survival after pidilizumab treatment was 9.3 months (range 6.8–24), median OS was 15.6 months (6.9–28), thus suggesting an improvement in survival. The results from this small study are preliminary, demonstrating that pidilizumab may be well tolerated and possibly active in pediatric patients with DIPG, although a larger sample size will be needed to further confirm these preliminary findings.

MICROENVIRONMENT

DIPG cells diffusely infiltrate the brainstem and brain, and they receive signals from multiple other cell types in this complex neural environment. The fact that DIPG arises at a particular time point during childhood and in a precise anatomical location indicates that there may be microenvironmental factors in the childhood pons that influence tumor initiation and growth. Oligodendrocyte precursor cells, a putative cell of origin for DIPG, are monopotent stem cells that self-renew and generate myelinating oligodendrocytes. Myelination of the central nervous system is a protracted process that extends over the first 3 decades of life, with predictable topographical and chronological patterns of myelination [84,85]. A discrete wave of ventral pontine myelination in mid-childhood correlates with the peak age of DIPG incidence [21,23].

Neuronal activity can regulate the proliferation of OPCs, resulting in generation of mature myelinating cells that fine-tune neural circuit function and contribute to adaptive changes in neurological function [86–89]. Activity-regulated secretion of brain-derived neurotrophic

factor (BDNF) is a key mechanistic component of adaptive myelination [90]. Activity-regulated mechanisms mediating brain plasticity and growth, such as BDNF, can be hijacked by glioma cells that utilize these signals for their own malignant proliferation.

Accordingly, glutamatergic neuronal activity promotes the proliferation and growth of DIPG and other HGGs [91] similar to the effects on the normal cellular counterparts. Two key glioma growth factors are released into the tumor microenvironment in response to neuronal activity - BDNF and, unexpectedly, a postsynaptic adhesion molecule called neuroligin-3 (NLGN3) that has been found to exert a profound effect on tumor proliferation [91]. NLGN3 not only promotes the growth of DIPG and other gliomas, it is required for glioma progression. Patient-derived xenografts of DIPG and other HGGs fail to progress when xenografted into the environment of the NLGN3-deficient brain [92■]. The reason for this surprising dependency on microenvironmental NLGN3 is presently a subject of intense study.

Although the binding partner for NLGN3 is currently unknown, future studies to elucidate and block the receptor or binding partner for NLGN3 may be an effective therapy. NLGN3 binding to this as-of-yet unidentified binding partner stimulates numerous oncogenic signaling pathways, including PI3K-mTOR pathway, Src, and Ras pathways in glioma cells to induce tumor proliferation. NLGN3 is cleaved by the metalloproteinase enzyme ADAM10, and secreted in a strictly activity-regulated manner by both OPCs (a postsynaptic cell type) and neurons. ADAM10 inhibitors prevent the cleavage and release of NLGN3 into the tumor microenvironment, and are thus an effective therapeutic strategy to limit tumor growth in preclinical models of DIPG and other HGGs [92■] (Fig. 1). A clinical trial is in preparation to test ADAM10 inhibition for children with DIPG.

Beyond activity-regulated protein secretion into the tumor microenvironment, several seminal studies have identified neurotransmitters and neuropep-tides that affect adult glioma cell behavior [93–95], although for the purposes of this review we will discuss mechanisms that have shown a role in DIPG. Certain H3K27M DIPGs have been shown to over-express the dopamine receptor D2, and other gliomas such as adult glioblastoma have demonstrated dopamine receptor-dependent growth [96,97]. A recent DIPG case report demonstrates improvement of clinical symptoms with the DRD2/3 antagonist ONC201 [98]. Glutamate also enhances the proliferation and invasion of glioblastoma cells through autocrine/paracrine signaling [99–102], and the effects of this neurotransmitter in DIPG is an area of active investigation. Underscoring the importance of neuron-glioma interactions, the ability of glioma cells to enhance excitability of surrounding neurons may act in a feed-forward mechanism to promote further secretion of protumorigenic factors [99,100].

CONCLUSION

DIPG is a complex tumor due to its molecular pathogenesis and epigenetic dysregulation, as well as critical influences of tumor microenvironmental signals that promote DIPG growth and progression. Additional challenges for DIPG therapy include a largely intact blood-brain barrier that is difficult to penetrate for drug delivery, and limited endogenous immune responses towards DIPG. No therapies for DIPG have proven curative thus far. Promising

therapies may involve harnessing distinct angles of DIPG vulnerabilities in combinatorial approaches to eradicate this heterogeneous tumor. Therapies that have been most promising in preclinical work or early clinical trials include epigenetic modifiers such as panobinostat, transcriptional regulators such as THZ1, CAR T immunotherapy, and microenvironmental targets such as ADAM10 inhibition. The enormous progress in understanding DIPG pathobiology, combined with advances in cancer neuroscience and immune-oncology give reason to hope that an effective therapeutic strategy will soon be realized.

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KEY POINTS

- DIPG is a relatively common pediatric brain malignancy with a median survival of ~10 months and 99% 5-year mortality.
- The H3K27M mutation found in the majority of DIPG cases causes epigenetic dysregulation and aberrant transcription that can be targeted therapeutically to limit expression of DIPG oncogenes.
- Targeting protumorigenic microenvironmental signaling may limit DIPG proliferation and represents an important strategy for therapy.
- Emerging immunotherapeutic approaches show promise.
- A combinatorial approach applying multiple therapeutic strategies may be necessary to eradicate this devastating pediatric tumor.

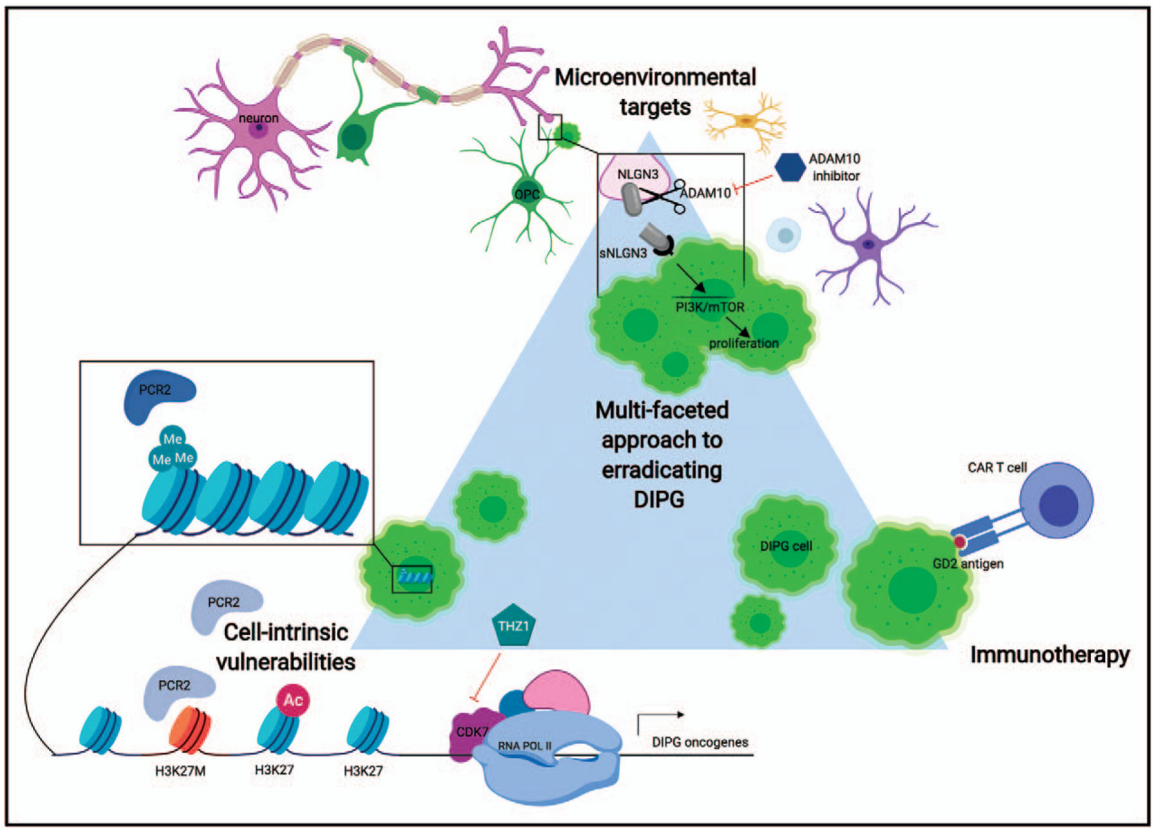

FIGURE 1.

Diffuse intrinsic pontine glioma is a heterogeneous tumor that lacks effective therapies. Eradicating this tumor may require a multifaceted approach with combinatorial therapies that target distinct tumor vulnerabilities. Here, we illustrate one therapeutic example in three distinct domains where studies have shown promising targeting of diffuse intrinsic pontine glioma. One cell-intrinsic therapy that targets the aberrant transcription resulting from H3K27M-mediated polycomb repressive complex-2 dysfunction is THZ1, an inhibitor of CDK7. CDK7 is responsible for phosphorylation of RNA pol II required for transcription initiation, and thus THZ1 may inhibit the increased transcription of diffuse intrinsic pontine glioma oncogenes that potentiates tumorigenesis. In immunotherapy, one of the most promising targets is the widely expressed diffuse intrinsic pontine glioma antigen GD2. Anti-GD2 chimeric antigen receptor T cells have demonstrated dramatic tumor clearance in xenograft models, and this strategy will be pursued in clinical trials. Diffuse intrinsic pontine glioma cells initiate and proliferate due to signals in the developing brain microenvironment, and strategies to inhibit protumorgenic signals will be important in containing tumor growth. Here, we illustrate the proliferation effect of neuronal-activity regulated neuroligin-3 secretion through the mammalian target of rapamycin (mTOR)/PI3K pathway. Inhibition of ADAM10 cleavage of neuroligin-3 prevents its activity-regulated secretion from neurons and oligodendrocyte precursor cells (OPCs) and causes a stark reduction in diffuse intrinsic pontine glioma proliferation. ADAM10 inhibitors will be used in future clinical trials for diffuse intrinsic pontine glioma. Diffuse intrinsic pontine glioma cells = neon green, neuron = pink, OPC = dark green, chimeric antigen receptor-T cell = purple, WT H3K27 histone =

light blue, H3K27M histone = orange, active polycomb repressive complex-2 = dark blue, inactive polycomb repressive complex-2 = gray, ADAM10 inhibitor = dark blue hexagon, THZ1 (CDK7 inhibitor) = turquoise pentagon. Illustration created using Biorender.