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Editorial

Identifying pediatric glioma's Achilles heel through rational combination therapies

Christopher G Hubert[1,2], Justin D Lathia[1,2,3]

[1]Department of Cardiovascular & Metabolic Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA; [2]Case Comprehensive Cancer Center, Cleveland, OH, USA; [3]Rose Ella Burkhardt Brain Tumor & Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH, USA

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Pediatric brain tumors are among the most lethal of pediatric cancers, with diffuse intrinsic pontine glioma (DIPG) one of the very worst. Prognosis for DIPG has remained relatively unchanged over the last several decades, and there are limited therapeutic options. Treatment includes radiation and a variety of chemotherapies, as surgical removal is next to impossible due to typical infiltration of the brain stem. Recent efforts have revealed key molecular alterations present in DIPG, including the common histone H3K27M mutation, which results in substitution of a methionine residue for lysine at amino acid 27 of histone H3. H3K27M is considered a driver of DIPG [1] and is now a molecular signature of diffuse midline gliomas according to the World Health Organization classification [2]. This mutation inhibits the activity of polycomb repressive complex 2 methyltransferase activity through interaction with EHZ2, which reduces methylation and leads to aberrant activity of a suite of putative oncogenes [3]. Given the specificity of the H3K27M mutation, it represents a next-generation molecular target for DIPG, and current approaches are generally focused on broad epigenetic inhibitors [4].

Related therapeutic efforts in brain tumors have focused on the imipridone family of molecules, of which ONC201 is a first-in-class brain-penetrant compound that induces apoptosis via the upregulation of tumor necrosis factor-related apoptosis inducing ligand (TRAIL) and pro-apoptotic death receptor (DR5) in a p53-independent manner [5]. ONC201 has been assessed in adult glioblastoma (GBM) and DIPG, with signs of efficacy in some patients [6], but the overall value of ONC201 in H3K27M DIPG is not clear, nor are the underlying mechanisms of ONC201 treatment effects in glioma. To directly address this, Brosuk *et al.* undertook a series of pre-clinical assessments of ONC201 and second-generation fluorinated derivatives (ONC206 and ONC212) in a series of DIPG models alone and in combination with epigenetic inhibitors and chemotherapies [7]. Using six DIPG patient-derived cell culture models, the authors found that ONC212 demonstrated the strongest efficacy, followed by ONC206 and ONC201. Mechanistically, treatment with ONC201 and its derivatives induced cell death via multiple mechanisms including DR5, the integrated stress response, and mitochondrial caseinolytic protease CLpP and its regulator, the caseinolytic mitochondrial matrix peptidase chaperone subunit X (CLPX). As DIPG patients are generally treated with chemotherapies and epigenetic inhibitors, the authors then tested ONC201, ONC206, and ONC212 in combination with such drugs. They found synergy with the histone deacetylate (HDAC) inhibitor panobinostat, the lymphoma chemotherapeutic romidepsin, and the proteasome inhibitor marizomib. Each imipridone showed similar synergy, though with minor disparities.

Tumor cell-specific induction of cell death has been a mainstay of cancer therapies, but clinical application has been challenged by the side effects of standard treatments and potentially limited therapeutic windows. Tumor-specific

mutations such as H3K27M provide an opportunity to exploit synthetic lethal interactions and evoke more specific cell death induction in the tumor tissue. ONC206 and ONC212 appear to be good candidates for DIPG based on these studies. It remains unclear how much of the efficacy is directly related to the H3K27M mutation, and the extent of a therapeutic window compared to normal neural cells has yet to be demonstrated. Future studies could directly interrogate these questions through in vitro assessment of isogenic H3K27M mutation models, as well as testing of ONC206 and ONC212 in neurons, astrocytes, oligodendrocytes, and microglia. While these in vitro assessments certainly identify potential combination therapies for future clinical trials, another immediate priority remains pre-clinical testing through accurate in vivo models. Immune-compromised models using human glioma xenografts (including the same six models used here) would be useful to measure preclinical efficacy. In addition, immune-component models would provide key information as to how the immune system is altered with ONC206 and ONC212 alone and in combination with other clinically relevant inhibitors, especially given the immunostimulatory activity of ONC201 [8]. This paradigm could be leveraged further for combination immunotherapies involving imipridones. Taken together, Brosuk *et al.* demonstrate that second-generation imipridones are likely more effective for DIPG as single agents compared to ONC201 and have set the stage for combination therapies. These studies are timely given the need for more effective DIPG therapies and the potential application of imipridones as anti-cancer therapies across a variety of tumor types.

Address correspondence to: Justin D Lathia, Department of Cardiovascular & Metabolic Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA; Case Comprehensive Cancer Center, Cleveland, OH, USA; Rose Ella Burkhardt Brain Tumor & Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH, USA. E-mail: lathiaj@ccf.org

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