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NEURO-ONCOLOGY

New therapeutic targets for diffuse intrinsic pontine glioma

Two studies published in *Nature Medicine* reveal new therapeutic targets for diffuse intrinsic pontine glioma (DIPG). These aggressive paediatric brainstem tumours are characterized by 5-year survival of only 1% after diagnosis. "It is a terrible disease without any good treatment options," comments Kristian Helin, corresponding author for one of the papers.

About 80% of DIPGs are associated with a lysine to methionine mutation in histone H3 (H3K27M) that inhibits methylation by polycomb repressive complex 2 (PRC2). However, some PRC2 methylation activity remains in tumour cells with this mutation, and the exact mechanisms that lead to tumour development are unclear, with different studies supporting oncogenic and tumour-suppressive roles for PRC2.

Both teams found that although PRC2 is inhibited in tumour cells from patients with DIPG, some PRC2 activity is required for tumour growth. Treatment of H3K27M-mutated tumour cells with inhibitors of the EZH2 catalytic subunit of PRC2 reduced cell proliferation, indicating that EZH2 inhibition presents a therapeutic strategy for DIPG.

> "Inhibition of EZH2 and bromodomain proteins are promising therapeutic strategies for DIPG"

Helin and colleagues showed that the protective effect of EZH2 inhibition is exerted through the tumour suppressor protein $p16^{INK4a}$. The *Ink4a* promoter was highly trimethylated in cells with the H3K27M mutation, and inhibition of EZH2 resulted in reduced methylation at this locus. Knockout of *Ink4a* in DIPG cell lines blocked the tumour-suppressive effects of EZH2 inhibitors on these cells.

Andrea Piunti and colleagues identified another pathogenic mechanism in H3K27M-mutated tumour cells. The team examined the status of histone H3 Lys27 residues across the genome using chromatin immunoprecipitation sequencing, and noted increased acetylation of these residues. Furthermore, the residues were bound by bromodomain proteins, which recognize acetylated lysine residues and participate in gene regulation. Treatment with bromodomain inhibitors reduced tumour growth in H3K27M-mutated cells, and also resulted in decreased tumour size and increased survival in mice injected with these cells.

These results suggest that inhibition of EZH2 and bromodomain proteins are promising therapeutic strategies for DIPG. Both teams emphasize that more research is needed to enable clinical translation of these approaches. "We need to show that EZH2 inhibitors can be used in a mouse model for DIPG and in xenograft models for human DIPG", explains Helin, who also cautions that we must ensure that the compounds can cross the blood–brain barrier. "If they do and we show preclinical proof of concept of these compounds in mouse models, EZH2 inhibitors should be ready for phase I clinical trials."

Piunti and co-authors Ali Shilatifard and Charles David James plan to investigate possible combination therapies and different drug delivery methods to facilitate extended remission for patients with DIPG. "Our co-author Rishi Lulla is working with industry partners to conduct a clinical trial to evaluate whether our preclinical observations on bromodomain inhibitor antitumour activity will translate into benefit for DIPG patients", comments James.

Charlotte Ridler

ORIGINAL ARTICLES Mohammad, F. *et al.* EZH2 is a potential therapeutic target for H3K27M-mutant pediatric gliomas. *Nat. Med.* http://dx.doi.org/10.1038/nm.4293 (2017) | Piunti, A. *et al.* Therapeutic targeting of polycomb and BET bromodomain proteins in diffuse intrinsic pontine gliomas. *Nat. Med.* http://dx.doi.org/10.1038/nm.4296 (2017)