Impact statement

Comparably little research has been done on the biology of paediatric glioma. Most laboratory studies have been conducted on cells deriving from adult glioma patients. However, it is becoming more and more clear that substantial differences exist between the adult and the paediatric form(1). For these reasons, I focused in my thesis on the investigation of paediatric low- and high-grade glioma. High-grade gliomas in children are generally associated with poor outcome(2,3). For certain entities, such as gliomas bearing a K27M mutation, the survival rates are close to 0%(4). One reason for the dismal course of disease is that a majority of paediatric high-grade gliomas are resistant to temozolomide, the standard chemotherapeutic agent used for the treatment of gliomas in adults(5,6). While the treatment of paediatric low-grade gliomas is successful in most cases, it is often connected with harsh (long-term) side-effects(7). This shows that there is a demand for new treatment approaches for both paediatric low- and high-grade gliomas.

Disulfiram is a drug with known safety profile and manageable side effects. In my thesis, I showed that both low- and high-grade paediatric glioma cell lines and patient-derived stem cells can be effectively killed by disulfiram. I detected that the drug targets the two epigenetic writers MLL1 and MLL2. By interfering with their enzymatic activity, disulfiram treatment disrupts multiple tumourigenic processes that I found to be regulated by MLL1 and MLL2. The improved understanding of the mechanism of action of disulfiram allows to screen for additional drugs that complement the effect of disulfiram. That way I detected that auranofin, a well-studied drug, enhances the killing efficacy and the MLL-targeting effect of disulfiram. Further, I found that the combined treatment with disulfiram and auranofin is especially effective against high-grade glioma cells that are less sensitive to disulfiram treatment. These findings highlight that disulfiram is of interest for the treatment of paediatric glioma in general, and that auranofin should be considered as an adjuvant in certain cases, e.g. when facing resistance.

The improved understanding of the biology of paediatric glioma might also help to tackle therapy resistance. I previously mentioned that a majority of paediatric high-grade gliomas are resistant to temozolomide treatment. Different genes and cellular pathways have been suggested as drug targets to improve the effect of the standard therapeutic treatment(8). I detected that MLL1 and MLL2 are involved in the regulation of multiple of these genes, and that disulfiram treatment leads to their downregulation. For this reason, I suggested that disulfiram might be used as an adjuvant to enhance the effect of temozolomide in resistant paediatric high-grade gliomas.

The dismal survival rates associated with K27 mutant gliomas show that there is a desperate need for drugs effective against these tumours. I demonstrated that K27 mutant glioma stem cells can be effectively treated with disulfiram and highlighted a potential mechanism of action. Deregulated gene expression is a hallmark of K27 mutant gliomas. I found that the knockdown of MLL1/MLL2 interfered with the aberrant gene expression signature in these cells. The same effect was achieved by disulfiram treatment. Thus, the drug might be suitable to normalise gene expression in K27M mutant cells, and to achieve a decrease in the tumourigenic potential of these highly aggressive gliomas. It is of interest to test disulfiram for the treatment of children suffering from K27 mutant gliomas.

To conclude, with my findings I contributed to the understanding of the biology of paediatric gliomas. I described a mechanism of action of disulfiram, and highlighted potential vulnerabilities of paediatric gliomas, including K27M mutant gliomas. This is not only of value for the scientific community but also for clinical research. It will now be of interest to translate my findings into medical practice. This might help to improve the survival rates of children with glioma and reduce the morbidity associated with the disease and the current standard treatment.

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