Chemoresistance in high-grade gliomas: relevance of adenosine signalling in stem-like cells of glioblastoma multiforme.


Abstract

Glioblastoma multiforme (GBM) is the most common glial cell-derived brain tumour, with one of the worst prognoses among all cancers. GBM cells are infiltrative and extremely resistant to radio- and chemotherapy, which inevitably leads to recurrence after surgical resection. These inherent GBM properties are the reasons that patient treatment has not seen major improvements in decades. Studies have consistently shown that glioblastoma stem-like cells (GSCs) are responsible for the tumourigenic properties in the GBM population. In fact, their self-renewal and proliferative potential are required for tumour growth, and their extreme chemoresistance leads to early recurrence of this tumour. Among those mechanisms associated with chemoresistance and having the greatest clinical impact in cancer treatment, are the activities of plasma membrane transporters that extrude antitumour drugs from the cell, thus notably decreasing the pharmacological efficiency of these drugs. The multiple drug resistance associated protein-1 (Mrp1) transporter has been shown to be particularly important in GBM, as inhibition of Mrp1 activity notably chemosensitises cells to antiproliferative drugs. As current therapeutic options for GBM offer only a poor improvement in overall survival rate, alternative strategies for overcoming tumour resistance are urgently sought after. To this end, it is of major clinical relevance to know more about the endogenous modulators that control Mrp1 expression within the pathological environment of the tumour. This review describes the particular properties of glioblastoma cells that overcome multimodal therapy and relapse, with an emphasis on the microenvironmental tumour properties that influence the chemoresistance phenotype to antiproliferative drugs. We also discuss alternative methods of reversal of Mrp1-mediated chemoresistance in these cells by targeting extracellular adenosine production or signalling through particular plasma membrane receptors.

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