Inibição da anidrase carbonica IX é importante no tratamento do glioblastoma: acidifica citoplasma e alcaliniza espaço peri-tumoral

Modulation of carbonic anhydrase 9 (CA9) in human brain cancer.


Source

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Abstract

Hypoxia is a crucial factor in tumour aggressiveness and its treatment resistance, particularly in human brain cancer. Tumour resistance against radiation- and chemo- therapy is facilitated by oxygenation reduction at tumour areas. HIF-1α regulated genes are mostly responsible for this type of resistance. Among these genes, carbonic anhydrase isoform 9 (CA9) is highly overexpressed in many types of cancer especially in high grade brain cancer like GBM. CA IX contributes to tumour environment acidification by catalyzing the carbon dioxide hydration to bicarbonate and protons, leading to the acquisition of metastasic phenotypes and chemoresistance to weakly basic anticancer drugs and therefore to inadequate application of radio-therapeutic or chemotherapeutic anti-cancer treatment strategies. Inhibition of this enzymatic activity by application of specific chemical CA9 inhibitors (sulphonamide derivative compounds) or indirect inhibitors like HIF-1α inhibitors (chetomin) or molecular inhibitors like CA9-siRNA leads to reversion of these processes, leading to the CA9 functional role inhibition during tumourigenesis. Hypoxia significantly influences the tumour microenvironment behaviour via activation of genes involved in the adaptation to the hypoxic stress. It also represents an important cancer prognosis indicator and is associated with aggressive growth, malignant progression, metastasis and poor treatment response. The
main objective in malignant GBM therapy is either to eradicate the tumour or to convert it into a controlled, quiescent chronic disease. Sulfonamide derivative compounds with CA9 inhibitory characteristics represent one of the optimal treatment options beside other CA9 inhibitory agents or chemical inhibitory compounds against its main regulating transcription factor which is the hypoxia induced HIF-1α when applied against human cancers with hypoxic regions like GBM, bearing potential for an effective role in human brain tumour therapeutic strategies. Glycolytic inhibitors, when added in controlled doses under hypoxia, lead to a reduced accumulation of HIF-1α and can function as indirect hypoxia regulated genes inhibitors like CA9. These may be used as alternative or in conjunction with other direct inhibitors like the sulphonamide derivate compounds, chetomin or specific siRNAs, or other different chemical compounds possessing similar functionality making them as optimal tools for optimized therapy development in cancer treatment, especially against human brain cancer. Further experimental analysis towards the tumour stage specific inhibitory CA9 characteristics determination are necessary to find the optimal therapeutic solutions among the different available modalities; whether they are direct or indirect chemical, molecular or natural inhibitors to be able to set up successful treatment approaches against the different human tumour diseases.

PMID:

20819065