Glioblastoma stem cell-driven recurrence radically changes tumor physiology, microenvironment and drug delivery via Gaussian shift.

Peter C Warnke MD; Sean Polster; Christoph B. Ostertag; Klaus Kopitzki MA
University of Chicago, Section of Neurosurgery, Chicago IL

Learning Objectives

To understand the contribution of tumor physiology in glioma stem cell driven tumor recurrence.

Introduction

Recurrent glioblastomas are highly resistant to treatment due to repopulation with glioma stem cells. We wanted to investigate whether these highly resistant cells also induce a vascular and extacellular microenvironment that contribute to therapeutic resistance

Methods

We have studied 7 GBMs before treatment and after recurrence. All patients underwent three-dimensional measurements of bidirectional capillary permeability, vascular volume , extracellular space and regional tumor blood flow before and after standard treatment. In addition a serial stereotactic biopsy was performed at recurrence to assess the glioma stem cell density. The physiological images were stereotactically coregistered with the biopsy sites to correlate physiological values with stem cell density.

Results

Capillary permeability was significantly increased from 23.9 +12.4 to 47.7+11.5 microl/g/min ($p<0.01$) and so was the size of the extracellular space (0.21 to 0.38.2 ml/g) in recurrent tumors ($p<0.01$). Blood flow was reduced from 43.3 +6.7 to 21.9+4.8 ml/g/min ($p<0.01$) almost reaching hypoxic tresholds. Histogram analysis of voxel distribution of physiological parameters showed that pretreatment values showed a Gaussian distribution whereas in recurrent tumors a complete shift towards extreme shoulders occur with for example higher K1 values and lower k2 values signifying a massive enlargement of extracellular space. Coregistration with biopsy sites showed that physiological variables were shifted the most towards excessive values in the vicinity of high density of glioma stem cells (Correlation coefficient $r=0.76$, $p<0.001$)

Conclusions

Glioma stem cells create a physiological niche around them characterized by large extracellular space and high permeability resulting in high interstitial pressure and low perfusion and hypoxia which form the physiological substrate of therapeutic resistance in human tumors.

Figures A and B - Blood Brain Barrier Permeability

This is an example of primary vs. recurrent tumor physiology with pretreatment showing a Gaussian distribution and recurrent tumors showing a complete shift towards extreme shoulders.