Growth Factors and Integrins Associated with Contrast-Enhancing Regions of GBM

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Introduction:

Glioblastoma multiforme (GBM) is a primary brain tumor with poor prognosis and low survival rate.[1-2] Similar to other types of solid tumors, GBM is heterogeneous in morphology with a high angiogenic component. Thus image-guided tissue sampling for microarray analysis is important in the identification of the most relevant molecular targets. Contrast-enhanced MRI (CE-MRI) using Gd(DTPA) has been demonstrated to be a powerful technique to identify regions with increased vascular permeability and vessel density.[3] In this study we proposed that CE-MRI can be used to guide tissue sampling for genomic analysis to identify angiogenic related growth factor and integrins family of heterodimeric proteins.

Materials and Methods:

Patients diagnosed with GBM, without any prior surgical, chemotherapy or radiotherapy procedures were scanned on a GE 1.5T MRI scanner using standard T1- and T2-weighted pulse sequences and Magnevist (Gd(DTPA), Berlex Inc., NJ) as contrast agent. Samples from regions that have contrast agent accumulation (contrast-enhancing, CE) and regions that do not take up contrast agent (non-enhancing, NE) were collected for gene expression profiling using oligonucleotide microarray (Figure 1). Genomic data was analyzed using a probe-level normalization package, Bioconductor®, to minimize variability, followed by a modified t-test via Significance Analysis of Microarray (SAM) for identifying significant expression levels.

Results:

Tissue samples from the CE and NE regions of 13 patients reveal significantly distinct gene expression patterns. Genes with high expression level in the CE region that are associated with integrins and growth factor family are selectively shown in Figure 2. These results show that integrins α_6, α_7, α_V, β_4, β_5, insulin growth factor binding proteins (IGFBP) 2, 3 and 5, platelet derived growth factor alpha (PDGFA), epidermal growth factor receptor (EGFR), and acidic fibroblast growth factor (aFGF) are all up-regulated in the CE regions as compared to the NE region. Immunohistochemical staining confirmed correlation of protein expression patterns with the observed genomic profile.

Conclusion:

We have observed that differences in spatial resolution within the tumor correlate to changes in gene expression profiles. We conclude that molecular features identified through image-guided microarray analysis correlating to the contrast enhanced regions in the tumor reveal the dynamic angiogenic status of the tissue. These molecular targets can be further screened to identify serum profiles for diagnostic and clinical monitoring of the patient before and after therapeutic intervention.
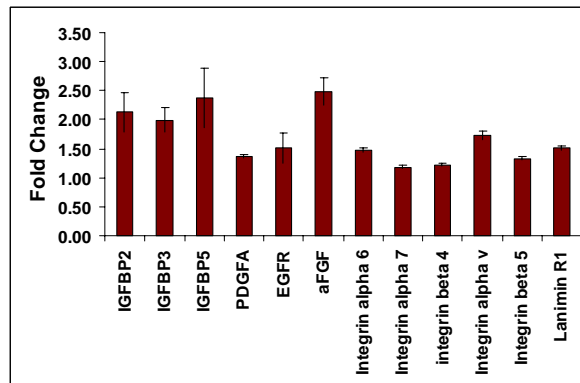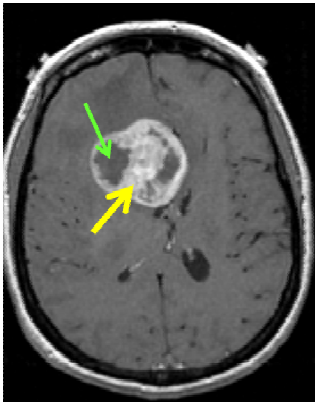
Figure 1 (Left). T-1 weighted CE-MRI of representative patient with GBM. The thick (yellow) and thin (green) arrows indicate the contrast-enhanced (CE) and non-enhanced (NE) regions, respectively.

Figure 2 (Right). Differential gene expression level (Fold change) between the contrast-enhanced (CE) and non-enhanced (NE) regions.

References:

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