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Tumor associated seizures in glioblastomas are influenced by survival gene expression in a region-specific manner: A gene expression imaging study

Jong Woo Lee[a,*], Andrew D. Norden[b], Keith L. Ligon[c,d], Alexandra J. Golby[e], Rameen Beroukhim[b], John Quackenbush[f], William Wells[g], Kristen Oelschlager[h], Derek Maetzold[h], Patrick Y. Wen[b]

[a] *Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, United States*
[b] *Center for Neuro-oncology, Dana Farber Cancer Institute, Harvard Medical School, 450 Brookline Avenue, Boston, MA 02115, United States*
[c] *Department of Pathology, Brigham and Women's Hospital, Boston Children's Hospital, and Harvard Medical School, 75 Francis Street, Boston, MA 02115, United States*
[d] *Department of Medical Oncology, Center for Molecular Oncologic Pathology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02115, United States*
[e] *Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, United States*
[f] *Department of Biostatistics, Dana Farber Cancer Institute, Harvard Medical School, 450 Brookline Avenue, Boston, MA 02115, United States*
[g] *Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA, United States*
[h] *Castle Biosciences Inc., 3330N 2nd Street, Suite 207, Phoenix, AZ 85012, United States*

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Summary Tumor associated seizures (TAS) are common and cause significant morbidity. Both imaging and gene expression features play significant roles in determining TAS, with strong interactions between them. We describe gene expression imaging tools which allow mapping of brain regions where gene expression has significant influence on TAS, and apply these methods to study 77 patients who underwent surgical evaluation for

* Corresponding author. Tel.: +1 617 732 7547; fax: +1 617 730 2885.
E-mail address: jlee38@partners.org (J.W. Lee).

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supratentorial glioblastomas. Tumor size and location were measured from MRI scans. A 9-set gene expression profile predicting long-term survivors was obtained from RNA derived from formalin-fixed paraffin embedded tissue. A total of 32 patients (42%) experienced preoperative TAS. Tumor volume was smaller (31.1 vs. 58.8 cubic cm, $p < 0.001$) and there was a trend toward median survival being higher (48.4 vs. 32.7 months, $p = 0.055$) in patients with TAS. Although the expression of only OLIG2 was significantly lower in patients with TAS in a groupwise analysis, gene expression imaging analysis revealed regions with significantly lower expression of OLIG2 and RTN1 in patients with TAS. Gene expression imaging is a powerful technique that demonstrates that the influence of gene expression on TAS is highly region specific. Regional variability should be evaluated with any genomic or molecular markers of solid brain lesions.

Introduction

Tumor associated seizures (TAS) are both common and debilitating (Hildebrand et al., 2005; Ruda et al., 2012). They are experienced by approximately half of the patients at some point, and about half of those will experience generalized tonic–clonic (GTC) seizures (Chang et al., 2008; van Breemen et al., 2007). TAS as well as the side effects from the use of antiepileptic drugs (AEDs) substantially contribute to morbidity (Hildebrand et al., 2005) and cause a marked decrease in the quality of life in patients with brain tumors (Klein et al., 2003; Moots et al., 1995; van Breemen et al., 2007). As advances in brain tumor treatments increase life expectancy, morbidity from TAS is becoming increasingly burdensome to the patient.

The mechanisms of TAS are incompletely understood and are likely multifactorial (Englot et al., 2012; Ruda et al., 2012; van Breemen et al., 2007). Previous neuroimaging studies demonstrated that tumor size and location play crucial roles in determining seizures related to tumors, and that these neuroimaging characteristics depend on the grade of the tumors. TAS are more likely to occur with smaller tumors in high grade tumors, and vice versa in low grade tumors (Lee et al., 2010). Tumors located in the cortex and in the temporal lobe are more likely to be associated with TAS than deeply seated tumors (Chang et al., 2008; Glantz et al., 1996; Liigant et al., 2001; Lynam et al., 2007; You et al., 2012a; Zaatreh et al., 2003).

Recently, dysregulation of glutamate control through the system x_c^- transporter (Buckingham et al., 2011) resulting in an increase of extracellular glutamate has been demonstrated to play a critical role in TAS in a mouse model. In human gliomas, increased system x_c^- expression and decreased expression of the membrane glutamate transporter protein EAAT2, also resulting in increased extracellular glutamate, has been demonstrated in patients with TAS (Yuen et al., 2012). In low grade tumors, abnormal expressions of several genes have been demonstrated from tumor and peritumoral tissue in patients with TAS (Niesen et al., 2013; You et al., 2012b).

Given that both gene expression and neuroimaging features are key characteristics in TAS, there is likely significant interaction between these critical features. In this study, we examine the expressions of 9 genes that are associated with long term survival (Colman et al., 2010). These genes may be of particular interest in TAS as the presence of seizures has been found to be a good prognostic factor in human gliomas (Okumus et al., 2012; Stark et al., 2012). We hypothesize that the influence of gene expression on TAS is regional, e.g. gene expression plays a significant role in determining epileptogenicity in certain regions of the brain whereas it plays little role in other regions where the location of tumor may predominate the determination of epileptogenicity. In regions where TAS is primarily determined by tumor location, we expect little influence of gene expression on TAS, whereas in other regions, gene expression may significantly affect TAS.

Materials and methods

Cohort selection

This retrospective study examined patients who underwent surgical evaluation of glioblastomas at the Brigham and Women's Hospital between January 2005 and September 2007. Inclusion criteria are as follows: age $\geq$18, new diagnosis of brain tumor, supratentorial location, pathologically proven glioblastomas, preoperative acquisition of high quality volumetric MRI scan, and the availability of a gene expression data on the tumor. Because gliomas with an oligodendroglial component are more prone to TAS (Wang et al., 2012), we excluded tumors with oligodendroglial components. Electronic medical records were reviewed by a board certified epileptologist (JWL) and patients were determined to have TAS if seizures were clinically present preoperatively. The AED regimen administered postoperative, chemotherapeutic regimen, and use of radiation therapy were recorded. Carbamazepine and phenytoin were considered enzyme inducing AEDs; none of the patients received phenobarbital. Survival duration was determined by the date of diagnosis by biopsy until date of death. Approval for this study was obtained from the local human research institutional review board and was performed using a combination of consent and waiver of consent where appropriate for minimal risk studies (Dana Farber Cancer Institute and Partners Healthcare Institutional Review Boards).

Image acquisition

Patients underwent preoperative imaging with one of two MRI scanners from which T2 and volumetric T1 images were obtained: 1.5 T General Electric Signa Excite scanner; 3 T General Electric Signa scanner.