The use of magnetic resonance imaging to guide the analysis of serum proteomic patterns in glioblastoma multiforme

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The purpose of this study was to investigate the relationship between serum and tissue proteomic patterns in distinct tumor regions from glioblastoma multiforme (GBM) patients, as identified by gadolinium contrast enhancement patterns on T1-weighted magnetic resonance (MR) images. We show that there are characteristic differences in the protein profile of serum from GBM patients versus normal controls. In particular, we have identified a group of low molecular weight peptides in the serum from GBM patients that are present in statistically higher concentrations than normal controls. The ability of MR imaging to identify tumor regions with increased permeability based upon contrast enhancement patterns holds promise for determining the identity of these serum peptides and their protein fragments.

Introduction

No serum biomarker for GBM currently exists and there is no simple method for following the disease course in patients to test new therapies. In previous studies, we showed that there are major differences in the protein expression patterns in the tumors of GBM patients that correlated with T1-weighted contrast-enhanced MR images. In particular, contrast-enhancing regions contained increased amounts of low-molecular weight peptides (1). These regions have also been shown in previous studies to have increased microvascular permeability (2). We hypothesized that the breakdown of the blood-brain barrier coupled with the high vascularity of GBM would result in the leakage of these low molecular weight peptides from contrast-enhancing tumor regions into the blood that we could detect using surface enhanced laser desorption/ionization time of flight mass spectroscopy (SELDI-TOF-MS). In this paper, we describe the first attempt to correlate serum proteomic patterns to tumor regions known to be permeable by MR imaging studies.

Materials and Methods

Patients with MR images and confirmed diagnosis of GBM were enrolled in the study. Images were acquired with a 1.5-T MRI scanner (GE Medical Systems, Milwaukee, WI) using a 28 cm × 28 cm field of view, and 2-mm interleaved slices. Precontrast spin-echo T1-weighted and fast spin-echo T2-weighted images were obtained. After the administration of a single bolus dose (0.1 mM/kg) gadopentate dimeglumine (Magnevist, Berlex Laboratories, Wayne, NJ), spin-echo T1-weighted (TR = 500 msec, TE = 30 msec, 16 kHz bandwidth, number of excitations (NEX) = 1) images were obtained. Sites for tissue sampling were determined by the neurosurgeons, neuroradiologists, and researchers, based on the postcontrast T1-weighted images (1). Prior to the initiation of therapy, serum samples were obtained from each patient. The protein expression profiles of the serum and tissue samples from contrast-enhancing and non-enhancing regions were assessed using immobilized metal affinity capture arrays (IMAC30, Ciphergen Biosystems, Fremont, CA) and SELDI-TOF-MS.

Results

We were able to identify a unique serum proteomic pattern for GBM. Four peaks of low molecular weight were statistically more intense in the mass spectrum of serum from GBM patients versus controls ($p<0.05$). These peaks were found at mass/charge ratios of 2792, 4286, 4503, and 5813 Daltons respectively (Figure 2). Proteins consistently found in higher concentration in the serum from GBM patients versus controls may potentially serve as biomarkers.

Conclusion

We have identified unique differences in the serum proteomic patterns between glioblastoma multiforme patients when compared to normal controls. The differences are consistent with our findings that contrast-enhancing tumor regions have increased quantities of low molecular weight peptides. Serum biomarkers for GBM are needed both to aid in diagnosis and to follow the course of therapy. Serum proteomic patterns have been identified in many types of cancer including ovarian, prostate, and breast. However, none of these studies have determined the identity of the serum biomarkers or where they originated. MR imaging is a technique we believe will aid in identifying permeable tumor regions which will aid in identifying serum biomarkers.

References

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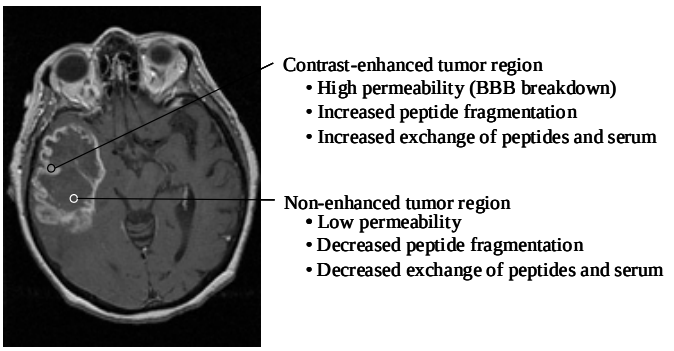

Figure 1. Post-contrast T1-weighted MR image from a patient with glioblastoma multiforme. The sites of tissue biopsy are indicated by the circles (black circle = contrast-enhanced region, white circle = non-enhanced region).

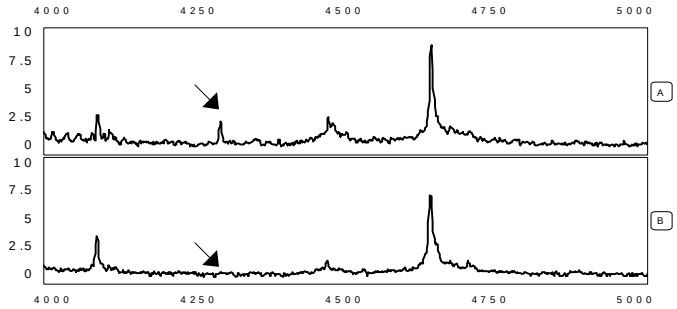

Figure 2. SELDI-TOF-MS spectrum of the serum from a glioblastoma multiforme patient (A) and a normal control (B). The region between 4000 and 5000 Daltons is shown. **(A)** The mass spectrum from the GBM patient contains a peak (arrow) at a mass/charge ratio of 4286. This peak was shown to be statistically more intense in the spectra from glioblastoma patients when compared to normal controls ($p<0.05$). **(B)** The corresponding SELDI-TOF-MS protein spectrum from the normal control without the described peak. Serum analysis for each patient was done in triplicate.