VEGFR2 expression in C6 and RG2 glioma models using molecular MRI

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Introduction

Angiogenesis is essential to tumor progression and metastasis and the precise imaging of angiogenic markers would provide accurate evaluation for angiogenesis [1, 2]. Vascular endothelial growth factor receptor 2 (VEGFR2) is an important active angiogenic marker which is over-expressed in many pathological conditions including malignant gliomas [3]. The goal of this study is to characterize varied angiogenesis status in C6 and RG2 glioma models by assessing expression of VEGFR2 using molecular magnetic resonance imaging (MRI).

Methods

Expression of VEGFR2 was assessed by intravenous administration of an anti-VEGFR2-albumin-Gadolinium (Gd)-DTPA-biotin probe to glioma-bearing rats. Control experiments were done with the administration of a control contrast agent of rat-IgG-albumin-Gd-DTPA-biotin.

Results

The results showed that VEGFR2 expressed heterogeneously in different regions in C6 gliomas, whereas was more relatively homogenous in RG2 gliomas (no significant differences were showed among different regions in RG2 gliomas). RG2 gliomas had less VEGFR2 expression, indicated by signal intensity changes in molecular MRI T_1 images, in tumor periphery and peri-necrotic regions, compared to C6 gliomas Fig. 1). However, RG2 gliomas had more VEGFR2 expression in the tumor interior region compared to C6 gliomas. The molecular MRI results were confirmed by fluorescence staining of the probe or control contrast agent 120 minute following administration (Fig. 2), which demonstrated that most of the anti-VEGFR2 probe targeted cellular expressed VEGFR2 on endothelial cells. Differentiation in VEGFR2 expression in C6 and RG2 gliomas suggest that C6 has more active angiogenesis regarding large blood vessels in the tumor periphery and peri-necrotic regions, and less angiogenesis related to small vessels or capillaries in the tumor interior compared to RG2 gliomas.

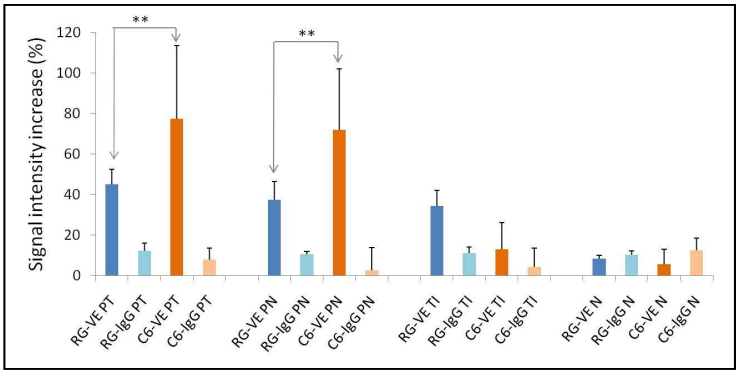

Figure 1: Comparison of signal intensity increase (%) induced by accumulation of the VEGFR2 probe at 120 min post injection between C6 and RG2 glioma-bearing rats. Signal intensities increase (%) were normalized to pre-injection signal intensity of T_1-weighted images. RG-VE PT indicates tumor periphery in the VEGFR2-probe injected RG2 rats, C6-IgG TI indicates tumor interior in the control-IgG agents injected C6 rats, and so forth. Significance were obtained using one way ANOVA with Tukey's multiple comparison test, with ** $p < 0.01$ showing significances between RG-VE PT and C6-VE PT, RG-VE PT and C6-VE PT.

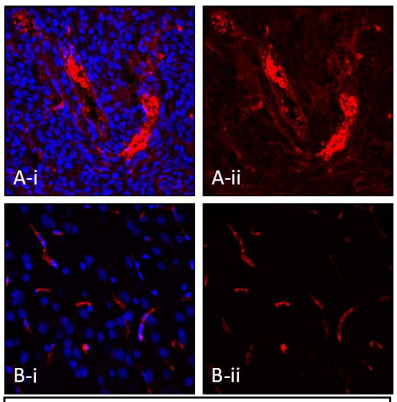

Figure 2: Fluorescence staining of the anti-VEGFR2 contrast agent in the RG2-glioma bearing brain tissue. The contrast agent was stained with Cy3-labeled streptavidin (red). The nuclei were stained with Dapi (blue). (A-i, ii) C6 gliomas injected with the VEGFR2 probe; (B-i, ii) Contralateral side of gliomas injected with the VEGFR2 probe.

Conclusion

In conclusion, the expression pattern of VEGFR2 using molecular MRI can be used as an accurate marker to evaluate active tumor-associated angiogenesis, and can be used to differentiate different angiogenic profiles in C6 and RG2 glioma models.

References

1. Vidal S, Kovacs K, Lloyd RV, *et al*. Angiogenesis in patients with craniopharyngiomas: correlation with treatment and outcome. *Cancer*. 2002; 94: 738-45.
2. Korkolopoulou P, Patsouris E, Kavantzas N, *et al*. Prognostic implications of microvessel morphometry in diffuse astrocytic neoplasms. *Neuropathol Appl Neurobiol*. 2002; 28: 57-66.
3. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev*. 2004; 25: 581-611.