A novel patient-specific model of glioma growth kinetics elucidates underlying biology as measured by gene expression microarray

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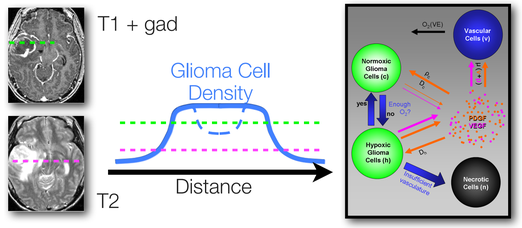
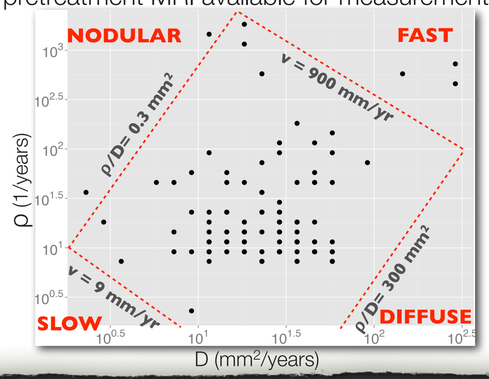
Measuring growth kinetics

Glioblastoma (GBM) is the most common primary brain tumor with universally poor prognosis. A hallmark of this disease is single-cell invasion into normal tissue. The kinetics of this invasion (D) and of cellular proliferation (ρ) can be estimated from routine pretreatment clinical imaging studies (MRI).



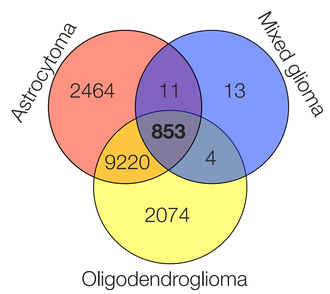
Distribution of kinetics

84 GBM patients with gene expression included in TCGA also had evaluable pretreatment MRI available for measurement.

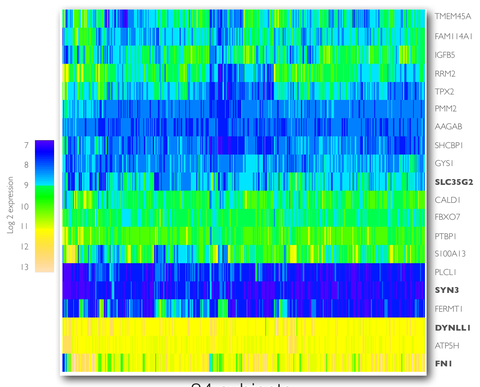


Differential gene expression of GBM patients with varying growth kinetics

REMBRANDT includes gene expression microarray data from 475 patients with glioma (grades II-IV). Differential gene of GBM versus lower grade disease reveals 853 genes whose expression are specific for GBM.

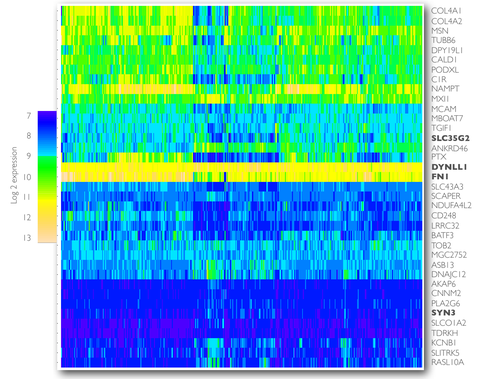


647 of these genes were also assessed in GBM patients in TCGA. Differential expression of 20 genes in a linear model of ρ are significant with an FDR < 0.05.



84 subjects

Performing differential expression of these genes in a linear model with D demonstrated 37 genes with a significant FDR < 0.05



84 subjects

Gene set enrichment analysis

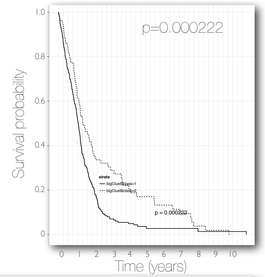
Gene set enrichment analysis with gene lists derived from the differential gene expression calculation revealed:

High D tumors are enriched for gene expression related to cell migration, integrin interactions and HIF activation with a relative reduction in genes related to focal-adhesions and extracellular matrix maintenance

High ρ tumors are enriched for genes related to resistance to therapy, induction after ionizing radiation and HIF pathway knock-down

Survival based on gene set

Building a classifier from these genes on 466 GBM patients in TCGA reveals two classes of patients with significantly different survival probability.



Conclusions

This work demonstrates the potential to assess underlying differences in biology in a heterogeneous disease from measurements of routine clinical imaging. We have previously shown that patients with high ρ tumors have worse survival, and here we find that these patients also differentially express genes related to treatment resistance and response to radiation. We have also found that patients with high D tumors demonstrate a decrease in gene expression related to focal adhesion and increase in motility genes.

Future work will validate these findings in external datasets and in biological specimens.

References:
[1]CH Wang, JK Rockhill, M Mrugala, et al. *Cancer Res* 2009;69:9133-9140
[2]M Szeto, G Chakraborty, J Hadley, et al. *Cancer Res* 2009;69:4502-4509

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