High field MRI characterization of tumor growth kinetics, vascularity and cellularity in a PDGF-driven *tv -a* mouse model of glioma

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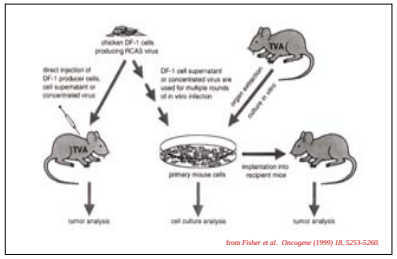
MOTIVATION

1. RCAS/tv-a technology provides a promising new platform for development of tissue-, and oncogenic pathway-specific mouse tumor models.
2. These models may facilitate elucidation of the mechanisms of neoplatistic transformation, development of targeted treatments.
3. MRI has unique capabilities in characterization of tumor appearance, growth and heterogeneity in transgenic mouse cancer models.
4. The nestin *tv*-a mouse model of glioma has never been characterized using high field MRI.

AIMS

1. To use high field (7T) MRI to characterize tumor appearance, heterogeneity and growth.
2. To characterize the development of tumor grade using contrast enhanced MRI.
3. To characterize tumor cellularity using diffusion MRI.
4. To correlate MRI findings with histology.

RCAS/*tv*-a TRANSGENICS



from Fisher et al. *Oncogene (1999) 18, 5253-5260.*

Conventional Transgenics

- Multi-gene defects require complex breeding patterns
- Germ line mutations often lethal to developing animal
- Organ specificity difficult to control

TVA Transgenics

- Control/introduction of multiple genetic defects in same model possible
- Somatic gene changes in adult animals
- Timing of defects more easily controlled
  - Simultaneous
  - Sequential
- Organ specificity controlled at multiple levels
  - Tissue specific promoters
  - Direct tissue virus infection
- One transgenic mouse for models of multiple genetic defects
  - Simplified breeding efforts

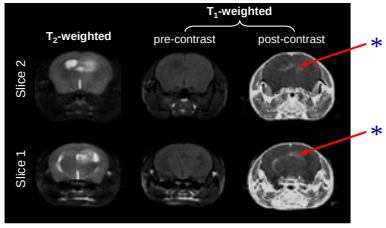
METHODS

- Mice expressing *tv-a* under the control of the nestin promoter expressed in glial-progenitors (*Ntv-a* mouse) [1] were bred.
- 19 *Ntv-a* mice that had developed tumors following intracranial injection with PDGF-encoding RCAS virus underwent weekly MRI to characterize tumor growth and development.
- T2-weighted fast spin-echo MRI was used to evaluate tumor growth.
- T1-weighted spin-echo MRI pre- and post-contrast agent injection, was used to delineate regions of dense and/or 'leaky' microvasculature.
- Tumor cellularity was also evaluated during the course of the study by diffusion-MRI measurement of the apparent diffusion coefficient (ADC).
- When signs of illness were apparent, animals were sacrificed, and the brains harvested for histology.

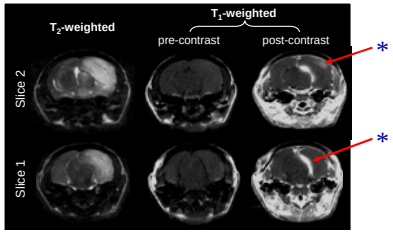
RESULTS AND CONCLUSIONS

Tumor Growth and Vascularity in the Ntv-a Mouse

Early Stage Glioma



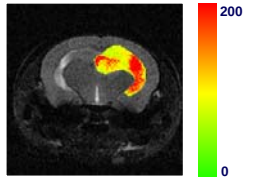
Late Stage Glioma



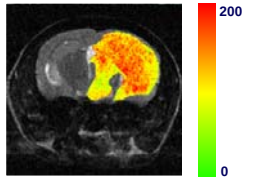
* localized post-contrast enhancing regions are indicative of leaky microvasculature typical of high grade glioblastoma multiforme

Tumor Cellularity: Diffusion MRI in the N*tv-a* Mouse

Early Stage Glioma

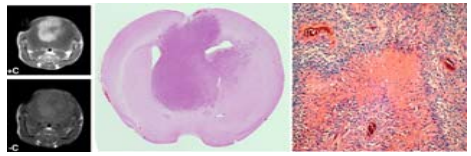


Late Stage Glioma



- ADC is inversely proportional to tumor cellularity
  - ⇒ high cellularity in tumor margins
  - ⇒ lower cellularity (high ADC) in the tumor core and ventricular regions

Histology



- Histology confirms the high cellularity typical of gliolbastoma multiforme

[1] Hesselager G, Holland EC. Review:Using mice to decipher the molecular genetics of brain tumors.Neurosurgery. 2003 Sep;53(3):685-94