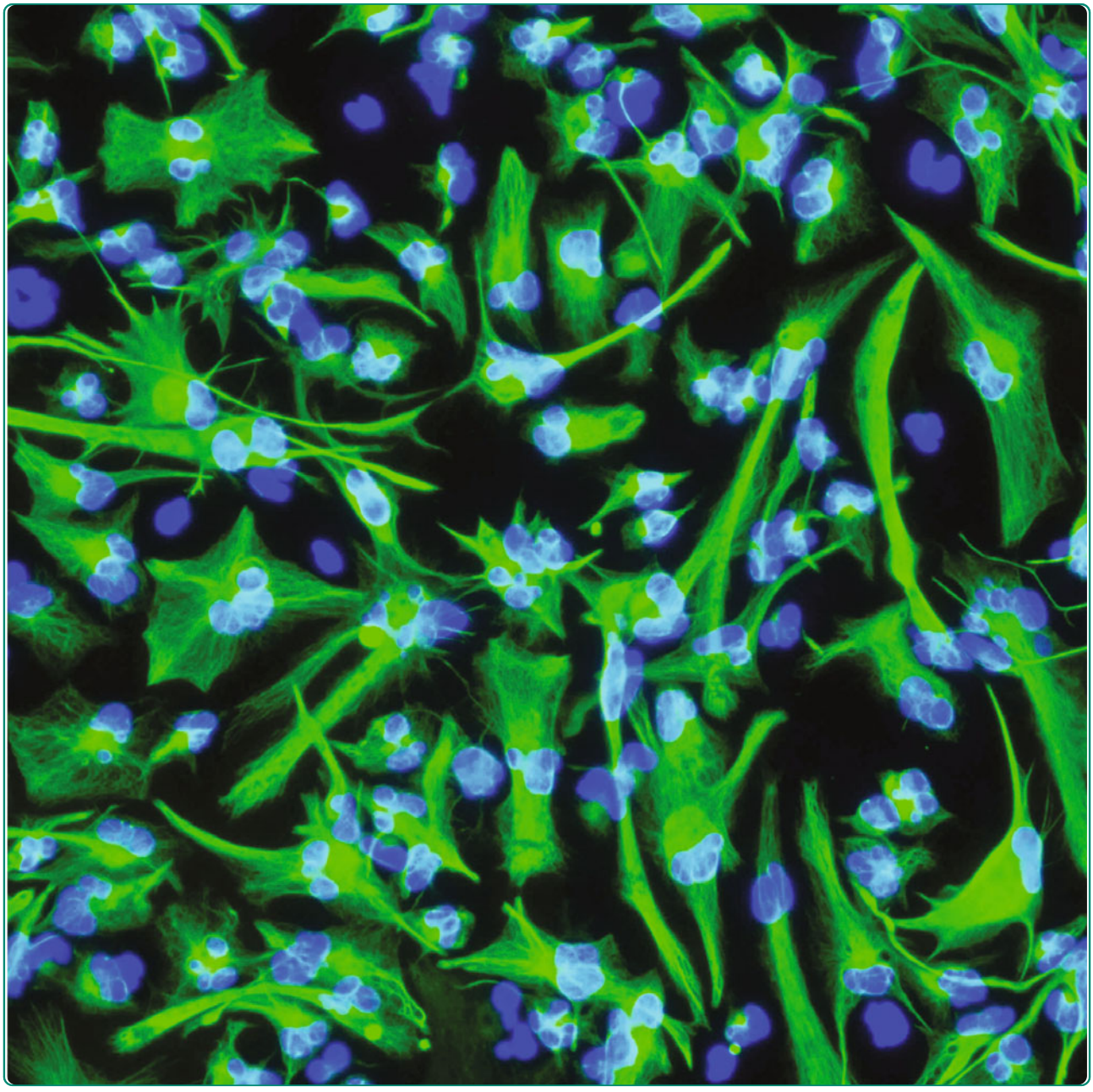
Genome Medicine



Digital transcriptome profiling of normal and glioblastoma-derived neural stem cells identifies genes associated with patient survival

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Digital transcriptome profiling of normal and glioblastoma-derived neural stem cells identifies genes associated with patient survival

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Abstract

Background: Glioblastoma multiforme, the most common type of primary brain tumor in adults, is driven by cells with neural stem (NS) cell characteristics. Using derivation methods developed for NS cells, it is possible to expand tumorigenic stem cells continuously *in vitro*. Although these glioblastoma-derived neural stem (GNS) cells are highly similar to normal NS cells, they harbor mutations typical of gliomas and initiate authentic tumors following orthotopic xenotransplantation. Here, we analyzed GNS and NS cell transcriptomes to identify gene expression alterations underlying the disease phenotype.

Methods: Sensitive measurements of gene expression were obtained by high-throughput sequencing of transcript tags (Tag-seq) on adherent GNS cell lines from three glioblastoma cases and two normal NS cell lines. Validation by quantitative real-time PCR was performed on 82 differentially expressed genes across a panel of 16 GNS and 6 NS cell lines. The molecular basis and prognostic relevance of expression differences were investigated by genetic characterization of GNS cells and comparison with public data for 867 glioma biopsies.

Results: Transcriptome analysis revealed major differences correlated with glioma histological grade, and identified misregulated genes of known significance in glioblastoma as well as novel candidates, including genes associated with other malignancies or glioma-related pathways. This analysis further detected several long non-coding RNAs with expression profiles similar to neighboring genes implicated in cancer. Quantitative PCR validation showed excellent agreement with Tag-seq data (median Pearson $r = 0.91$) and discerned a gene set robustly distinguishing GNS from NS cells across the 22 lines. These expression alterations include oncogene and tumor suppressor changes not detected by microarray profiling of tumor tissue samples, and facilitated the identification of a GNS expression signature strongly associated with patient survival ($P = 1e\text{-}6$, Cox model).

Conclusions: These results support the utility of GNS cell cultures as a model system for studying the molecular processes driving glioblastoma and the use of NS cells as reference controls. The association between a GNS expression signature and survival is consistent with the hypothesis that a cancer stem cell component drives tumor growth. We anticipate that analysis of normal and malignant stem cells will be an important complement to large-scale profiling of primary tumors.

Background

Glioblastoma (grade IV astrocytoma) is the most common and severe type of primary brain tumor in adults. The prognosis is poor, with a median survival time of 15 months despite aggressive treatment [1]. Glioblastomas display extensive cellular heterogeneity and contain a population of cells with properties characteristic of neural stem (NS) cells [2]. It has been proposed that such corrupted stem cell populations are responsible for maintaining cancers, and give rise to differentiated progeny that contribute to the cellular diversity apparent in many neoplasias. Data supporting this hypothesis have been obtained for several types of malignancies, including a variety of brain cancers [2]. Importantly, a recent study using a mouse model of glioblastoma demonstrated that tumor recurrence after chemotherapy originates from a

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