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Molecular classification of glioma stem cells

Comprehensive genetic analysis of glioblastomas by The Cancer Genome Atlas (TCGA) has proposed a new classification based on genetic abnormalities. The characteristic genetic abnormalities identified in the TCGA are promising candidates for novel molecularly targeted therapies, and further studies are warranted. In this study, we performed a comprehensive analysis of 25 glioma stem cell lines and compared them with TCGA data to elucidate their molecular biological characteristics.

To classify glioma stem cell subtypes, gene expression analysis was performed on 25 glioma stem cell lines using two different methods. First, we performed supervised clustering using the 1461 probe set used in the four-subtype classification of glioblastoma. One cluster was further classified into two subclusters with elevated expression of “proneural” genes, and the other into two subclusters with elevated expression of “classical” genes and “mesenchymal” genes, respectively. The other was classified into two subclusters with elevated expression of “classical” and “mesenchymal” genes, respectively. The proneural subcluster was classified into one with elevated expression of “neural” genes and one with elevated expression of “proneural” genes. Unsupervised clustering using the top 1600 probe sets4) resulted in the same four subclusters as in supervised clustering (Fig. 1).

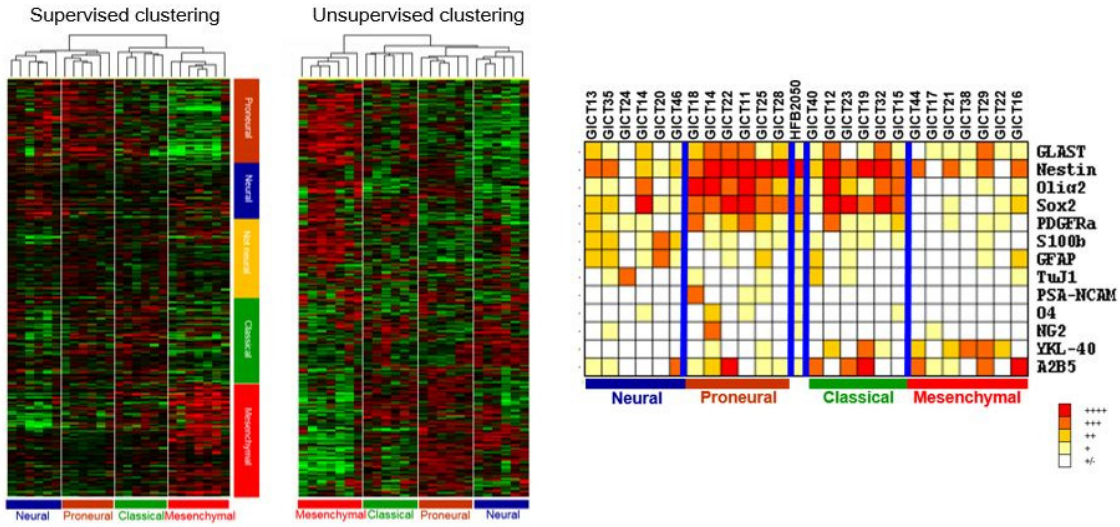

Fig. 1. Glioma stem cells are classified into four subtypes: proneural, neural, classical, and mesenchymal. Glioma stem cells show different differentiation potential depending on the subtype.

We analyzed the expression of neuronal differentiation markers in each subtype by immunostaining. Glioma stem cells showed different expression trends of neuronal differentiation markers and different different differentiation directions (neural and mesenchymal). Neural stem cell markers such as Sox2, Olig2, and Nestin were highly expressed in proneural and classical types, while astrocytic markers such as GFAP and

S100 β were highly expressed in neural type. The glial markers A2B5 and GLAST were highly expressed in proneural and classical types. In addition, the proneural and classical types are thought to maintain a more primitive stemness, whereas the neural type shows a differentiation tendency.

The proneural and classical types of glioma stem cells showed the ability to differentiate into three lineages: astrocytic, neuronal, and oligodendrocytic. The neural type showed resistance to astrocytic and neuronal lineages, and the mesenchymal type showed resistance to differentiation medium.

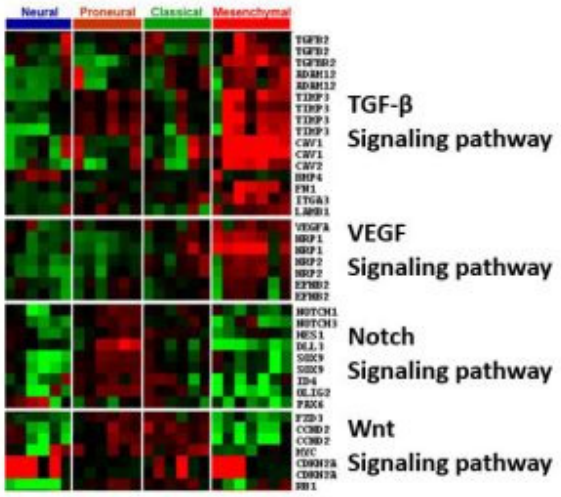

Fig. 2. Signaling pathways in glioma stem cells.

Glioma stem cells exhibited subtype-specific lineage markers and differentiation potentials, which is reminiscent of the hierarchical normal neural development process in which signaling pathways (e.g., the Notch and Wnt pathways) are differentially tuned. ANOVA analysis was used to identify genes that were significantly differentially expressed among subtypes. The genes identified overlapped with a manually curated gene list comprising known genes involved in the Wnt, Notch, and TGF-signaling pathways, which revealed differential activation and deactivation of signaling pathways. In mesenchymal type, the TGF-pathway component was highly expressed, concurrent with deactivation of Notch and Wnt, as physiological inhibitors of Notch and Wnt are abundant in this subtype. Notch pathway components were highly enriched in classical and proneural type but deactivated in neural type (Fig. 2). These results indicate that glioma stem cells may be maintained in different signaling pathways in different subtypes, which may be useful data for the development of new therapies targeting glioma stem cells.

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Publication

Genetic and Lineage Classification of Glioma-Initiating Cells Identifies a Clinically Relevant Glioblastoma Model

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