Journal of Cell Science & Therapy

Iwadate, J Cell Sci Ther 2014, 5:5
DOI: 10.4172/2157-7013.1000182

Commentary Open Access

Malignant Progression of Glioblastoma

Yasuo Iwadate*

Department of Neurological Surgery Chiba University Graduate School of Medicine, Chiba, Japan

***Corresponding author:** Yasuo Iwadate, Department of Neurological Surgery, Graduate School of Medicine, Chiba University, 1-8-1, Inohana, Chuo-ku, 260-2870 Chiba, Japan, Tel: 81-43-226-2158; Fax: 81-43-226-2159; E-mail: iwadatey@faculty.chiba-u.jp

Rec date: Sep 03, 2014; **Acc date:** Sep 26, 2014; **Pub date:** Sep 29, 2014

Commentary

Glioblastoma (GBM) is the most devastating type of human cancers with a median survival time ranging from 12-18 months following maximal therapies [1]. Glioma is classified into four malignancy grades according to histological features; the low-grade tumors including WHO Grade I (localized gliomas) and WHO Grade II (diffuse astrocytoma or oligodendrogliomas), and the high-grade tumors including WHO Grades III (anaplastic gliomas) and WHO Grade IV (GBM). The concept of malignant progression is usually applied to secondary GBM which is originally a grade II or grade III glioma and is diagnosed as GBM at the time of recurrence. Most of this tumor carries IDH1 mutation, in contrast to primary GBM without carrying isocitrate dehydrogenase-1 (IDH1) mutation which is the majority of GBM [2]. Although GBM is considered to be a final stage of tumorigenesis collecting many types of genetic alterations in the oncogenes and tumor suppressor genes, large variations of survival time exist within the same category of GBM. Recently, the Cancer Genome Atlas (TCGA) showed that GBM can be categorized into four subclasses based on molecular genetic properties, which is partially relevant to patient survival [3]. The proneural subtype is associated with a good prognosis, and neural, classic, and mesenchymal subtypes are identified [3]. The mesenchymal subtype is characterized by neo-angiogenesis and highly-invasive nature, leading to poor prognosis [3,4]. Non-mesenchymal subtypes usually acquire the gene expression pattern of mesenchymal subtype at recurrence after chemotherapy and radiotherapy [4]. One of the most striking features of mesenchymal subtype is the expression of stem cell markers [3,4]. Actually, glioma cells that express stem cell markers are highly invasive and resistant to radiotherapy and chemotherapy in vitro and in the clinical setting [5]. The heterogeneous survival periods of GBM patients may reflect the acquisition of mesenchymal features or stem cell properties on the course of disease progression.

Such a phenotypic change in cancer tissue may be caused by various stimuli from cancer microenvironment. Differentiated cells can change their phenotype under the influences of repair-associated or pathological stresses. One phenomenon that facilitates such dynamic reprogramming of the cellular state is epithelial-mesenchymal transition (EMT) [6]. EMT is a biological process that induces a polarized epithelial cell to undergo multiple biochemical changes into mesenchymal phenotype including enhanced migratory capacity and elevated resistance to genotoxic insults. EMT is also known as an important inducer of cancer stem cells. The shift toward mesenchymal phenotype of GBM after various therapies at recurrence suggests the contribution of EMT activated in hypoxic microenvironments and tissue repair processes [7]. Since GBM usually contains large areas of necrosis, many GBM of mesenchymal subtype would have progressed from other subtypes in the natural course of the disease. The stem cell phenotype may be induced by EMT-related transcription factor network through epigenetic regulations, which contributes to the poor prognosis of GBM. The “malignant progression of GBM” can be a main target of future therapies for GBM.

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