Glioblastoma Multiforme

Highly malignant, invasive, difficult-to-treat primary brain tumor

Frequency: 9,000 cases/year (peak age, 55–65 years)

Recurrence: rapid growth; size may double every 10 days

Median survival: ~ 1 year
Survival of adult patients with glioblastoma multiforme
Pediatric Brain Tumors

Frequency: 3000 cases/year
Pediatric brainstem glioma

- Brainstem location represents 8-15% of all brain tumors in the pediatric population.

- Usually inoperable tumors because of the particular location in the brain.
Survival for Children with Diffuse Pontine Gliomas (CCG 9941)

J Clin Oncol 20:3431-3437, 2002
Tumor cells multiply which results in growth
Normal growth is controlled
Why do tumor cells grow?

Tumor cells receive the instructions to grow but are insensitive to instructions to stop.
Propagation of neural stem cells

Blue: nucleus

Green: nestin

Nestin: marker of stem cells
Differentiation of neural stem cells in neurons and glia

Blue: nucleus
Green: GFAP astrocytes
Red: β-IIIITub neurons
Brain development requires a controlled switch from proliferation to differentiation.
Disruption of pathways essential for neurogenesis have been implicated in childhood and adult brain cancers, for which immature progenitor cells have been proposed as cells-of-origin
Id proteins: inhibitors of differentiation

Undifferentiated state

- High growth potential
- High amounts of Id proteins

Differentiated state

- Low growth potential
- Low amounts of Id proteins

Iavarone and Lasorella, 2003
Id proteins are antagonists of transcription factors

- **No Id proteins**

- **Id proteins in functional excess**

Activation of transcription and differentiation

Inhibition of transcription and block of differentiation
The Rb-Id2-bHLH pathway in pediatric tumors
Normal cells

Cancer cells

Cancer cells invade normal tissues

Wild type Rb
Id2 inactive

Mutant Rb
Id2 hyperactive
Id2 loss impairs tumor growth and angiogenesis in tumors from Rb+/- mice.
Id proteins are coexpressed with HIF1\(\alpha\) in human glioblastoma
Id2 overexpression in neuroblastoma is associated with reduced survival.

Overall study population

Id2 negative, n=18
Id2 positive, n=29

P=0.0046
Id proteins involved in all processes associated with development of neural tumors:

- **VEGF Signaling**
  - Integrins, MMP2
  - Angiogenesis
  - Anaplasia

- **Id**

- **Metalloproteinases**
  - Tissue Invasion
  - Proliferation

- **Lineage Specific bHLH**

- **Rb, bHLH, Ets, Pax**
THE FUTURE: Anti Id2 therapeutics

- Growth arrest
- Differentiation
- Increased cell death
- Inhibition of angiogenesis
Underlying challenge: how to control stem cells
Control brain tumor/neural stem cell behavior

N-Myc

Stem cell

Huwe1

N-Myc

Glia

Neuron
Loss of Huwe1 expands the neural stem cell population

**Huwe1\(^{F/Y}\)**

**Huwe1\(^{F/Y}\) Nes**
Loss of Huwe1 impairs neural stem cell differentiation

$Huwe1^{F/Y}$

$Huwe1^{F/Y}Nes$

Nestin/DAPI

$\beta$III-tubulin/DAPI
Focal deletions and decreased expression of \textit{Huwe1} in GBM

Normal brain \(n=23\)  GBM \(n=77\)

P-value: \(9.3\times10^{-10}\)
Expression of Huwe1 is lost in primary neuroblastomas displaying accumulation of N-Myc protein
Neural stem cell

Growth factors → N-Myc → Lineage commitment
Differentiation
Cell cycle arrest

Huwe1

Growth arrest
Maturation

CD2

p27

N-Myc

Tumor stem cell

Tumor growth

Growth factors
Malignant gliomas invade the normal brain
The mesenchymal signature of high-grade glioma

Unsupervised clustering of 76 high grade tumors by expression of 108 genes that are positively or negatively associated with survival reveals 3 tumors classes - Proneural (PN), Mesenchymal (Mes) and Proliferative (Prolif).

Malignant gliomas belonging to the mesenchymal sub-class express genes linked to the most aggressive properties of glioblastoma (migration, invasion and angiogenesis) and mark the worst clinical outcome.
The mesenchymal network of six major hubs of transcription factors in high-grade gliomas
STAT3 and C/EBPβ inhibit neuronal differentiation and induce mesenchymal transformation in neural stem cells.
Knockdown of Stat3 and C/EBPβ cooperates to inhibit tumor cell invasion and angiogenesis.
Loss of Stat3 and C/EBP\(\beta\) in human glioma cells inhibits tumorigenesis in the mouse brain

Human glioma-shCtr

Human glioma-shStat3+shC/EBP\(\beta\)

Cumulative Survival

Days post-injection

Cumulative Survival

Days post-injection
The combined expression of Stat3 and C/EBPβ correlates with the poorest outcome of glioma patients.

![Survival curve with Kaplan-Meier estimator](image)

- **Positive Stat3 + C/EBPβ**
- **Negative Stat3 + C/EBPβ**

*Statistical significance: $p < 1 \times 10^{-3}$*
Glioblastoma
From systems biology to prognosis to personalized therapy

Mesenchymal Signature Of High Grade Glioma

ARACNe Regulatory Network

Stat3 and C/EBPβ are Master Regulators
Stat3 and C/EBPβ are Transforming Oncogenes of Neural Stem Cells
Stat3 and C/EBPβ are Predictors of Negative Clinical Outcome
The integrated landscape of driver genomic alterations in glioblastoma

Genomic targets/signatures

A new classification of human lower grade glioma

Molecular pathway

Diffuse grade II and III (lower-grade) gliomas
- IDH mutation
  - 226 cases
- 1p/19q codeletion absent
  - 141 cases
- IDH wild type
  - 56 cases

Molecular alteration

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Clinical presentation

LGG
- LGG: frequent
- GBM: rare

LGG
- LGG: rare
- GBM: frequent

Integrated molecular multi-platform analysis of 1,122 glioma from multiple sources

*IDHmut* LGG/G-CIMP segregate into two independent groups according to the extent of DNA methylation: G-CIMP-*high* and G-CIMP-*low*

DNA methylation analysis identified a subgroup of *IDHwt* LGG (PA-like) which is enriched for somatic *NF1* mutations and a more favorable survival

Therapeutic targeting of gene fusions in cancer

CML

Overall survival (%)

Months after beginning treatment

Druker B. 2009

NSCLC

Overall survival (%)

Time (years)

Shaw A. 2011
• The FGFR3-TACC3 gene fusions were first discovered in glioblastoma (GBM) (Singh et al., Science 2012).

• FGFR-TACC fusions were subsequently found in many other human tumors.

• FGFR-TACC is the most frequent chromosomal translocation occurring in human cancer with a lower bound estimate of at least 12,000 new patients per year in USA harboring this gene fusion.
Response to JNJ-42756493 in patients with recurrent GBM harboring FGFR3-TACC3 fusion -44%
FGFR-TACC fusions are powerful predictors of clinical response to FGFR inhibitors

4 of 5 with FGFR3-TACC3