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-III Tub 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**

  bHLH heterodimer

  Activation of transcription and differentiation

- **Id proteins in functional excess**

  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 HIF1α 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
- Metalloproteinases
- Angiogenesis
- Anaplasia
- Tissue Invasion
- Proliferation
- Lineage Specific bHLH
- Rb, bHLH, Ets, Pax
THE FUTURE: Anti Id2 therapeutics

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

- N-Myc
- Huwe1
- 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\textsuperscript{F/Y}  

\textbf{Nestin/DAPI}

\textbf{βIII-tubulin/DAPI}

\textbf{Huwe1\textsuperscript{F/Y Nes}}

\textbf{Nestin/DAPI}

\textbf{βIII-tubulin/DAPI}
Focal deletions and decreased expression of *Huwe1* in GBM

Normal brain: n=23  GBM: n=77

P-value: 9.3E-10
Expression of Huwe1 is lost in primary neuroblastomas displaying accumulation of N-Myc protein
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.

Vector

Untreated

20 days
Knockdown of Stat3 and C/EBPβ cooperates to inhibit tumor cell invasion and angiogenesis
Loss of Stat3 and C/EBPβ in human glioma cells inhibits tumorigenesis in the mouse brain.
The combined expression of Stat3 and C/EBPβ correlates with the poorest outcome of glioma patients.
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

Mesenchymal Signature Of High Grade Glioma
ARACNe Regulatory Network

Glioblastoma
From systems biology to prognosis to personalized therapy

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

ARACNe Regulatory Network
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
- 1p/19q codeletion present: 85
- 1p/19q codeletion absent: 141
- IDH wild type: 56

Molecular alterations

Inactivating
- CIC
- FUBP1
- NOTCH1

Activating
- PIK3CA
- PTBP1
- TERT
- IDH1
- IDH2
- TP53
- ATRX
- MYC
- CCND2
- IDH1
- IDH2
- PTEN
- NF1
- CDKN2A
- EGFR
- MDM4
- TERT

Clinical presentation

LGG
- LGG: frequent
- GBM: rare

LGG: rare
- GBM: frequent

A New Methylation-based Pan-Glioma Classification

- Integrated molecular multi-platform analysis of 1,122 glioma from multiple sources
- *IDH*mut 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 *IDH*wt LGG (PA-like) which is enriched for somatic *NF1* mutations and a more favorable survival

Therapeutic targeting of gene fusions in cancer

**CML**

- Chromosome 9
- Chromosome 22
- Philadelphia-Chromosom
- 9q34.12
- ABL
- 22q11.21
- BCR

**NSCLC**

- ALK
- Exon 20
- EML4
- Exon 13
- EML4-ALK

**Overall survival (%)**

- Months after beginning treatment
- Druker B. 2009

**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.

Yoshihara et al. Oncogene 2015
Response to JNJ-42756493 in patients with recurrent GBM harboring FGFR3-TACC3 fusion
FGFR-TACC fusions are powerful predictors of clinical response to FGFR inhibitors

4 of 5 with FGFR3-TACC3