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

Kaplan-Meier Survival Curves

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

Brain development requires a controlled switch from proliferation to differentiation

Neurogenesis and Brain tumors

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

Id proteins: inhibitors of differentiation

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
  - bHLH heterodimer
  - Inhibition of transcription and block of differentiation

The Rb-Id2-bHLH pathway in pediatric tumors

Rb → ID → bHLH → G1/M

IGF, EWS-Ets, Myc, bHLH, S, G1, S, G2, M, p57, Kip2
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

Survival (percentage)

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<th>Time (months after diagnosis)</th>
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P=0.0046

Id proteins involved in all processes associated with development of neural tumors

VEGF Signaling

Integrins, MMP2

Angiogenesis

Anaplasia

Lineage Specific bHLH

Id

Metalloproteinases

Tissue Invasion

Proliferation

Rb, bHLH, Ets, Pax