Molecular Genetics of Brain Tumors

Deepa S. Subramaniam, M.D., M.Sc.
Director, Brain Tumor Center
Lombardi Comprehensive Cancer Center
Georgetown University, Washington DC

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Translational neuro-oncology

Brain Tumors

Medulloblastoma

Ependymoma

Low grade Glioma

Glioblastoma
Objectives

- To analyze medulloblastoma subtypes, and delve into the genetics of standard risk medulloblastoma (SHH subtype), and targeted therapies in development

- To recognize the distinct molecular subtypes in ependymoma, and correlation with age, prognosis and potential therapeutic implications

- To elucidate the impact of genomic profiling on prognosis, risk stratification and impact on treatment recommendations in gliomas
Medulloblastoma
Medulloblastoma

- Most common solid neoplasm in children
- High grade, aggressive
- **Standard vs high risk:**
  - Age <3 years
  - Incomplete resection
  - Metastasis at Dx
  - LC/Anaplastic histology
Medulloblastoma Sub-types:

**Classic**
- WNT signaling
- CTNNB1 mutation
- Monosomy 6
- Good prognosis
- Low risk
- 5-yr survival 94%

**Desmoplastic/classic**
- SHH signaling
- PTCH1/SUFU/SMO mutations
- Intermediate prognosis
- Standard risk
- 5-yr survival 87%

**LC/Anaplastic**
- GROUP 3
  - Photoreceptor/GABAergic signaling
  - TGF-b signaling
  - Poor prognosis
  - Very high risk
  - 5-yr survival 32%

**LC/Anaplastic**
- GROUP 4
  - Glutamatergic/NFkB signaling
  - Intermediate-poor prognosis
  - High risk
  - 5-yr survival 76%

Age Distribution - Medulloblastoma
Sonic Hedgehog Protein

DESERT HEDGEHOG PROTEIN

SONIC HEDGEHOG PROTEIN

INDIAN HEDGEHOG PROTEIN
A Tale of Three Friends

Sonic Hedgehog (SHH)

SMOOTHENED (SMO)

PATCHED1 (PTCH)

Knuckles
SHH

PATCH1

SMO

GLI Proteins
SHH signaling in Medulloblastoma

12 Years...
Ependymomas
Ependymomas

- Arises from ependymal cells lining ventricles or spinal canal
- Grow exophytically into ventricle → obstruction → hydrocephalus
- Characteristic pseudo-rosettes
- Stains for GFAP and EMA
Ependymomas

Supratentorial ependymoma

Posterior fossa ependymoma

Spinal ependymoma
Supratentorial

- ST-SE: Subependymomas: balanced genome
- ST-EPN: RELA Fusions $\rightarrow$ drives NF-$\kappa$B signaling
- ST-EPN: YAP1 fusions $\leftarrow$ YAP1 downstream of SHH

Posterior Fossa

- PF-SE: Subependymomas: balanced genome
- PF-EPN-A: balanced genome, CIMP-positive, very poor outcome
- PF-EPN-B: chromosomal instability

Spinal

- SP-SE: Subependymoma: 6q deletion
- SP-MPE: Myxopapillary ependymoma (chromosomal instability)
- SP-EPN: NF2 mutation

Defining the Molecular Landscape of Ependymomas

Tenley C. Archer¹,² and Scott L. Pomeroy¹,²,*


SP-SE 1%  SP-MPE 5%  SP-EPN 4%  PF-SE 7%
ST-EPN-YAP1 3%  ST-EPN-RELA 18%  ST-SE 4%
PF-EPN-B 10%  PF-EPN-A 48%

Survival five:

<table>
<thead>
<tr>
<th></th>
<th>Spine</th>
<th>Posterior Fossa</th>
<th>Supratentorial</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP-SE</td>
<td>49</td>
<td>59</td>
<td>40</td>
</tr>
<tr>
<td>SP-MPE</td>
<td>32</td>
<td>3</td>
<td>1.4</td>
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<td>SP-EPN</td>
<td>41</td>
<td>30</td>
<td>8</td>
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<tr>
<td>PF-SE</td>
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<td></td>
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<tr>
<td>PF-EPN-A</td>
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<td>PF-EPN-B</td>
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<tr>
<td>ST-SE</td>
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<tr>
<td>ST-EPN-YAP</td>
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<tr>
<td>ST-EPN-RELA</td>
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</tbody>
</table>

Median age at diagnosis (years):

49  32  41  59  3  30  40  1.4  8
Gliomas
WHO grading

Atypia/Mitoses

Geographic necrosis/
Pseudopalisading

Endothelial proliferation
The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary

David N. Louis¹ · Arie Perry² · Guido Reifenberger³,⁴ · Andreas von Deimling⁴,⁵ · Dominique Figarella-Branger⁶ · Webster K. Cavenee⁷ · Hiroko Ohgaki⁸ · Otmar D. Wiestler⁹ · Paul Kleihues¹⁰ · David W. Ellison¹¹

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Defining Risk – Low Grade Gliomas

* Age >40 years
* Tumor size > 6 cm
* Tumor crossing the corpus callosum
* Astrocytic histology
* Presence of neurologic deficits before surgery

Pignatti JCO 2002
WHO Grade I tumors

- Pilocytic astrocytoma (PA)
- Ganglioglioma (GG)
- Pilomyxoid astrocytoma (PMA)
- Pleomorphic xanthoastrocytoma (PXA)

**Most common genetic aberrations**

- BRAF fusions
- BRAF V600E mutations
WHO Grade II/III tumors

**IDH1/2 mutant**
- 1p/19q co-deleted
  - Oligodendroglioma (Type I)

**IDH1/2 wildtype**
- No 1p/19q co-del
  - Diffuse Astrocytoma (Type II)
- ATRX loss
  - Anaplastic Astrocytoma (Type III)
LOW RISK
Age <40 AND GROSS TOTAL RESECTION
Arm 1 = Observe

HIGH RISK
Age >40 OR SUBTOTAL RESECTION/BIOPSY
Stratify by:
Oligo-dominant Vs. Astro-dominant; KPS; Age; Enhancement

RANDOMIZE

Arm 2 = Radiation Therapy (54 Gy/30 fractions)

Arm 3 = Radiation Therapy
PCV x 6 cycles
CCNU 110 mg/m² (day 1)
PCBZ 60 mg/m² (days 8-21)
VCR 1.4 mg/m² (days 8 & 29)

(2.0 mg cap)
### RTOG 9802 – Final Results

<table>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th>RT alone</th>
<th>RT + PCV</th>
<th>Hazard Ratio</th>
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<tbody>
<tr>
<td>PFS</td>
<td>4 yrs</td>
<td>10.4 yrs</td>
<td>0.50 (significant)</td>
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<tr>
<td>PFS-IDH mutant</td>
<td>-</td>
<td>-</td>
<td>0.32 (significant)</td>
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<tr>
<td>OS</td>
<td>7.8 yrs</td>
<td>13.3 yrs</td>
<td>0.59 (significant)</td>
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<tr>
<td>OS-IDH mutant</td>
<td>-</td>
<td>-</td>
<td>0.42 (significant)</td>
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Final Recommendations
WHO Grade 2 Gliomas

* High risk low grade gliomas
  - All patients should get 6 cycles of adjuvant PCV following partial brain RT to 50.4 Gy
  - Benefit is greater in patients whose tumors who are IDH-mutant
IDH mutations – Oncogenic Drivers?
IDH mutations – Oncogenic Drivers?

Krebs’ Cycle

Tumor cell

Mitochondrion

Citrate → Isocitrate → IDH1 → αKG → 2-HG → IDH2 mutant

Epigenetic changes

Impaired cellular differentiation

BAY1436032

IDH305
WHO Grade III Gliomas
RTOG 9402: Grade 3 Gliomas

OS in Overall Population

OS by 1p/19q Status

1p/19q co-deleted: survival improved from 7 yrs to 14 yrs with addition of PCV
## Final Results - RTOG 9402 (WHO Grade 3 Gliomas)

<table>
<thead>
<tr>
<th></th>
<th>Median OS (yrs)</th>
<th>Median OS (yrs)</th>
<th>Median PFS (yrs)</th>
<th>Median PFS (yrs)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Co-del</td>
<td>No co-del</td>
<td>Co-del</td>
<td>No co-del</td>
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<tr>
<td></td>
<td>7.3</td>
<td>2.7</td>
<td>2.9</td>
<td>1.0</td>
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<tr>
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<td>14.7</td>
<td>2.6</td>
<td>8.4</td>
<td>1.2</td>
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</table>
CATNON: WHO grade 3 AA (non co-deleted)

RESULTS:
Median PFS: A/B: 19 mo, C/D: 42.8 mo
Median OS: A/B: 41 mo, C/D: Not reached
5 yr survival: A/B: 44.1%, C/D: 55.9%
Final Recommendations

* WHO Grade 3 Glioma
  * Co-deleted 1p/19q: Adjuvant radiation → 6 cycles PCV
  * Not co-deleted: Concurrent chemoradiation with temozolomide → 12 cycles adjuvant temozolomide
Glioblastoma
WHO Grade IV tumors

Glioblastoma (IDH wild type)

Primary GBM
Loss of multiple tumor suppressors (TP53, RB1, NF1)
Overexpression of growth factors (EGFR, RAS, BRAFV600E, CDKN2A)

Secondary GBM ← De-diff from astrocytoma
TP53 Loss
ATRX loss
CDKN2A Loss
PTEN mutation
TMZ in Newly Diagnosed GBM:

- **TMZ 200 mg/m²/d x 5 days, repeat every 28 days**
- **TMZ 75 mg/m²/d x 7 days for 6 - 7 wks**
- **Cycle 1**
- **Cycle 2**
- **x 6 cycles**
- **Focal RT (30 x 2 Gy, 60 Gy)**
  Tumor volume with 2 - 3 cm margin

*Stupp NEJM 2005*
MGMT methylation – A Predictive Marker

Hegi ME et al. NEJM 2005
06-Methylguanine-DNA Methyltransferase (MGMT)

- TMZ, methylating agent

**MGMT Gene**
- located on CHR 10q26
- encodes DNA repair enzyme
- removes methyl-groups from O6-alkylguanine
- linked with resistance to alkylating agent therapy

• irreversible inactivation
• degradation
*MGMT* repair gene silencing by gene promoter methylation

- Tumor: methylated → no expression
  - Promoter region
  - *MGMT GENE* expression
- Normal: no methylated → expression

Tumor grows

**Tumor**
- No repair protein
- No repair of TMZ treatment induced DNA damage

- Response to tumor treatment
- Improved survival of glioblastoma patient
Keep Marching On...