Epigenetic addiction in pediatric brain tumours

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WIN 2014
Disclosures

• Nothing to disclose
What about Brain Tumours in children?

- Brain tumours are the first cause of death related to cancer and the most common solid tumour in children.
- Progress has been made for specific sub-groups including medulloblastomas and ependymomas.
- Lifesaving therapies have unacceptable morbidities.
- Limited breakthroughs have been made for HGA and subgroups of embryonal tumours which remain deadly human cancers.
US cancer incidence from Surveillance, Epidemiology, and End Results (SEER), 1975 to 1998, by CNS tumor type.
Children are not small adults

- Tumor type
- Tumor location within the brain
- Tumor microenvironment
- Tumor history
- Tumor biology even when tumor looks the same
What are the known Molecular Pathways in High Grade Gliomas?
Adult gliomas

- Glial progenitor cells → IDH1 mutation (>85%)
- Common precursor cells
- TP53 mutation (>65%)
- Loss 1p/19q (>75%)
- Diffuse astrocytoma → Oligodendroglioma

Pediatric gliomas

- Ras-BRAF-RAF1 mutation/fusion
- NF1 loss → Pilocytic astrocytoma (grade I)
- Low-grade astrocytoma (grade II)
- Anaplastic astrocytoma (grade III)
- Primary GBM (grade IV)

Absence of stepwise progression from lower grade to higher grade
Distinct molecular alterations
“These results identify changes to chromatin structure and the resulting gene expression patterns as a driver for these aggressive pediatric tumors. Furthermore, they provide a much-needed new pathway that can be targeted for therapeutic development.”


from Pediatrics: Sequencing the Next Generation

Pediatric glioblastomas driven by epigenetic changes

Laurie Gay Cell 148: 1074 (March 16, 2012)
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What is histone H3F3A?

H3.3 N-terminal tail

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H3F3B  H. sapiens  11  STGGKAPRKQLATKAARKSAPSTGKVKKPHRYRPGTVLAREIRRYQKSTE  60
HIST1H3A  H. sapiens  11  STGGKAPRKQLATKAARKSAPATGKVKKPHRYRPGTVLAREIRRYQKSTE  60
H3f3c  M. musculus  11  STGGKAPRKQLATKATRKASAPSTGKVKKPHRYRPGTVLAREIRRYQKSTE  60
His3.3B  D. Melanogaster  11  STGGKAPRKQLATKAARKSAPSTGKVKKPHRYRPGTVLAREIRRYQKSTE  60
Hht3  S. Pombe  11  STGGKAPRKQLASKAARKSAPATGKVKKPHRYRPGTVLAREIRRYQKSTE  60
AT1G13370  A. thaliana  11  SHGGKAPTKQLATKAARKSAPTTGKVKKPHRYRPGTVLAREIRKYQKSTE  60

The nucleosome is the fundamental unit of chromatin

Heterochromatin (silent)

Euchromatin (active)

H2A
H2B
H3
H4

Luger, Richmond and colleagues *Nature* 1997
The hallmarks of cancer comprise six biological capabilities acquired during the multistep development of human tumors. The hallmarks constitute an organizing principle for rationalizing the complexities of neoplastic disease. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis.

The hallmarks of Cancer, Hanahan and Weinberg, Cell 2011
Structural component of nucleosomes: packaging of DNA.

Actively involved in the regulation of chromosomal accessibility and gene expression:
- DNA Replication
- RNA Transcription
- Telomere maintenance
- Functional organization of the nucleus

Agnes Coquet & Genevieve Almouzni 2007

Barcoding Life
“Histone code”

• Type and amount of histone to be loaded
• Preferential loading during specific stages of development and specific tissues:
  • Synthesis according or not to the cell cycle
  • (canonical, non canonical)
• Chaperone loading the histone
• Post translational modifications of the histone tails;
H3.3

• Non-canonical histone: production and loading are cell-cycle independent

• Replacement histone and loading is enriched in areas of active transcription

• The predominant histone 3 to be loaded in the nucleosomes of
  • telomeres
  • the developing brain
H3.3 mutations are location and age-dependent

Sturm et al (Jabado & Pfister, Cancer Cell 2012)
Dkhuong-Quang (Jabado, Hawkins, Acta Neuropathologica 2012)
Sturm et al (Jabado & Pfister, Cancer Cell 2012)
ATRX is an H3.3 chaperone
Deposition of histone variant H3.3 is mediated by ATRX-DAXX

Elsasser et al. Science 331, 1145(2011)
ATRX mutations characterize IDH-TP53 astrocytomas

**ASTROCYTOMAS**

- **IDH**
  - **TP53**
  - **ATRX**

**OLIGODENDROGLIOMAS**

- **IDH**
  - CIC-FUPBP 1p/19p loss
  - Tert promoter mutations

EPIGENETIC INSULT

CELL CYCLE DAMAGE

TELOMERE LENGTHENING

Liu et al (Jabado), Acta Neuropathologica 2012
Jiao et al Oncotargets 2012
Adult HGG: Pathways in gliomagenesis

- Glial progenitor cells
- IDH1 mutation (>85%)
- Common precursor cells
- TP53 mutation (>65%)
- Loss 1p/19q (>75%)

**TP53 mutation**
- EGFR amplification (~35%)
- TP53 mutation (~30%)
- PTEN mutation (~25%)
- NF1 alteration (~20%)
- LOH 10p (~70%)
- LOH 10q (~70%)

**Diffuse astrocytoma**
- Anaplastic astrocytoma
- Anaplastic oligodendroglioma

**Oligodendroglioma**

**Primary glioblastoma**

**Secondary Glioblastoma**

**TERT promoter**

**ATRX**

Age > 50 years

Age < 50 years
Pediatric and Young Adult astrocytomas are a story of 2 lysines: K27 and K36
Recurrent somatic mutations in ACVR1 in pediatric midline high-grade astrocytoma


Recurrent activating ACVR1 mutations in diffuse intrinsic pontine glioma

Kathryn R Taylor, Alan Mackay, Nathalene Truffaux, Yaron S Butterfield, Olena Morozova, Cathy Philippe, David Castell, Catherine S Grasso, Maria Vincenzi, Diana Carvalho, Angel M Carcaba, Carmen de Torres, Ofelia Cruz, Jaume Mora, Natasha Entz-Werle, Wendy J Ingram, Michelle Monje, Darren Hargrave, Alex N Bullock, Stephanie Puge, Stephen Yip, Chris Jones & Jacques Grill

The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma


Genomic analysis of diffuse intrinsic pontine gliomas identifies three molecular subgroups and recurrent activating ACVR1 mutations

Pawel Buczko, Christine Hoeman, Patricia Rakopoulos, Sanja Pajovic, Louis Letourneau, Misko Dzamba, Andrew Morrison, Peter Lewis, Eric Bouffet, Ute Bartels, Jennifer Zuccaro, Sameer Agnihotri, Scott Ryall, Mark Barszczewski, Yevgen Chornenyk, Mathieu Bourgeois, Guillaume Bourque, Alexandre Montpetit, Francisco Cordero, Pedro Castelo-Branco, Joshua Mangerell, Uri Taborsky, King Ching Ho, Annie Huang, Kathryn R Taylor, Alan Mackay, Anne B Bendel, Javad Nazarian, Jason R Fangusaro, Matthias A Karajannis, David Zaggag, Nicholas K Foreman, Andrew Donson, Julia V Heger, Amy Smith, Jennifer Chan, Lucy Lafay-Cousin, Sandra Dunn, Juliette Hukin, Chris Dunham, Katrin Scheinemann, Jean Michaud, Shayan Zelcer, David Ramsay, Jason Cain, Cameron Brennan, Mark M Souweidane, Chris Jones, C David Allis, Michael Brudno, Oren Becher & Cynthia Hawkins.
42 midline and 43 cerebral cortex treatment naive HGA
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<th>Gene</th>
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Cortical HGA-HGG
Cerebral Cortex: K36

- SETD2
- IDH/TP53
- G34R/V H3.3/TP53
- H3.3/TP53
- H3.3/FGFR
- H3.3/TP53
- H3.1/ACVR1

Midline: K27M

- AGE
- ATRX
- NO HTERT

Medulloblastoma
EZH2, KDM6A

Posterior Fossa ependymoma
PRC2 signature

Cerebellum and Spine

Brainstem (DIPG)

Thalamus

CORTEX

Brainstem (DIPG)
Epigenome modulation and Epigenetic addiction

- Previously unsuspected way of oncogenesis
- Tumours are “locked” in a specific state that promotes survival and potentially spread
- Plasticity
- Addicted:
  - Homogeneity across tumours
  - Homogeneity within tumours
  - Recurrences almost identical
- Harder to target?
NGS, Robotics and models, extensive collaborations, and the Integration of public datasets and knowledge

BEFORE

NOW

NEAR FUTURE

FAST, EFFICIENT, HIGHLY SPECIFIC

AFFORDABLE, COST EFFECTIVE

MAJOR CHANGE IN THE COMPREHENSION - DIAGNOSIS - FOLLOW UP

MOLECULAR PATHOLOGY

www.biocomicals.com
Acknowledgements

ATID PED132
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