

SPOTLIGHT

Harnessing brain development to understand brain tumours

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ABSTRACT

Brain tumours are the commonest solid neoplasms in children, accounting for one quarter of all childhood cancers. Our growing knowledge of basic developmental mechanisms has significantly contributed to understanding the pathogenesis of these tumours and is beginning to impact clinical decisions on how children with these diseases are treated.

KEY WORDS: Diffuse intrinsic pontine glioma, Ependymoma, Medulloblastoma, Paediatric tumours

Introduction

Brain development is characterised by the neatly orchestrated interplay of intrinsic and extrinsic cellular cues. These cues elicit a broad array of cell processes including proliferation, differentiation, communication, migration and death that together define spatiotemporal diversity within the developing brain. Paediatric brain tumours comprise temporally and topographically distinct subtypes (Fig. 1, Table 1). Thus, the roots of these diseases have long been suspected to lie in specific cell lineages within the developing brain. Cross-species genomic analyses of human tumours and developing mouse brain, coupled with genetic mouse modelling, have implicated specific cell lineages as the origin of a number of childhood brain tumours and have shown how deregulated developmental mechanisms play a role in the pathogenesis of these tumours. Here, we focus on three of the most common and challenging paediatric brain tumours – medulloblastoma, ependymoma and diffuse intrinsic pontine glioma (DIPG) – as examples of how understanding of developmental lineages and mechanisms has advanced significantly our understanding of these devastating cancers.

Medulloblastoma

Medulloblastoma, a malignant hindbrain tumour, was once considered a single entity. However, extensive genome-wide DNA and RNA sequencing by numerous groups have since divided medulloblastoma into four subgroups, each with distinct origins, genomic drivers and clinical outcomes (for a recent review see Hovestadt et al., 2020). SHH-medulloblastoma, which are fatal within 5 years in 25% of cases, contain activating mutations in the SHH pathway and arise from cerebellar granule neuron progenitor cells (Marino et al., 2000; Yang et al., 2008). In contrast, WNT-medulloblastoma are curable even when metastatic, contain activating mutations in *CTNNB1* and arise from mossy fibre precursor cells of the lower rhombic lip (Gibson et al., 2010). Single

cell sequencing of the developing mouse hindbrain has validated these earlier findings and provided insights into the origins of the two other medulloblastoma subtypes – group 3 and 4 medulloblastoma (Hovestadt et al., 2019; Vladoiu et al., 2019). Cells of group 3 medulloblastoma, which kill around half of all patients, resemble nestin⁺ cerebellar progenitor cells; whereas cells of group 4 medulloblastoma, a subgroup containing complex genetic and epigenetic drivers (Badodi et al., 2017; Northcott et al., 2009) and which is fatal in 25% of cases within 5 years of diagnosis, resemble the cerebellar unipolar brush (UBC) lineage. Of note, cells with developmental signatures reminiscent of nestin⁺ and UBC⁺ progenitors coexist within a proportion of group 3 and 4 medulloblastoma, suggesting overlap in lineage origins of these less well-defined subgroups (Hovestadt et al., 2019).

Demonstrating that the different subgroups of medulloblastoma arise within distinct hindbrain lineages has provided a road map for understanding the pathogenesis, diagnosis and treatment of these tumours. For example, genetic mouse modelling has shown that *Ddx3x* – one of the most frequently mutated genes in medulloblastoma – regulates hindbrain development by controlling Hox expression and restricts the susceptibility of different hindbrain lineages to the mutations that drive WNT- or SHH-medulloblastoma (Patmore et al., 2020). The distinct developmental origins of medulloblastoma are also now considered during patient diagnosis: radiological location of medulloblastoma in the midline attached to the dorsal brainstem or lateral cerebellar hemisphere supports a diagnosis of WNT- or SHH-medulloblastoma, respectively. Ongoing research is targeting malignant processes in transformed mossy fibre and granule neuron lineages as potential new treatments of medulloblastoma.

Ependymomas

Ependymomas, the third most common type of childhood brain tumour, arise throughout the central nervous system (CNS) and display distinct, site specific, clinical behaviours. Similar to studies of medulloblastoma, cross-species transcriptome studies of ependymoma and developing mouse brain pinpointed radial glia in different regions of the CNS as candidate cells of origin of forebrain, hindbrain and spinal ependymoma (Taylor et al., 2005). Targeting topographically discrete radial glia in mice with mutations observed in the corresponding type of human ependymoma generated accurate models of ependymomas, validating radial glia lineage as the origin of the disease (Johnson et al., 2010; Mohankumar et al., 2015). Recent comparisons of single cell RNA sequences of developing mouse brain and human tumours have confirmed that ependymomas are transcriptionally related to radial glial progenitors (Vladoiu et al., 2019). Gene enhancer, super enhancer and transcriptome profiling have also identified radial-glia-derived progenitor cells committed to the ependymal lineage – the ciliated epithelial cells that line the ventricles – as potential cells of origin of ependymoma (Mack et al., 2018). Extensive genome-wide DNA sequencing, methylome and transcriptome studies of large numbers of human ependymomas

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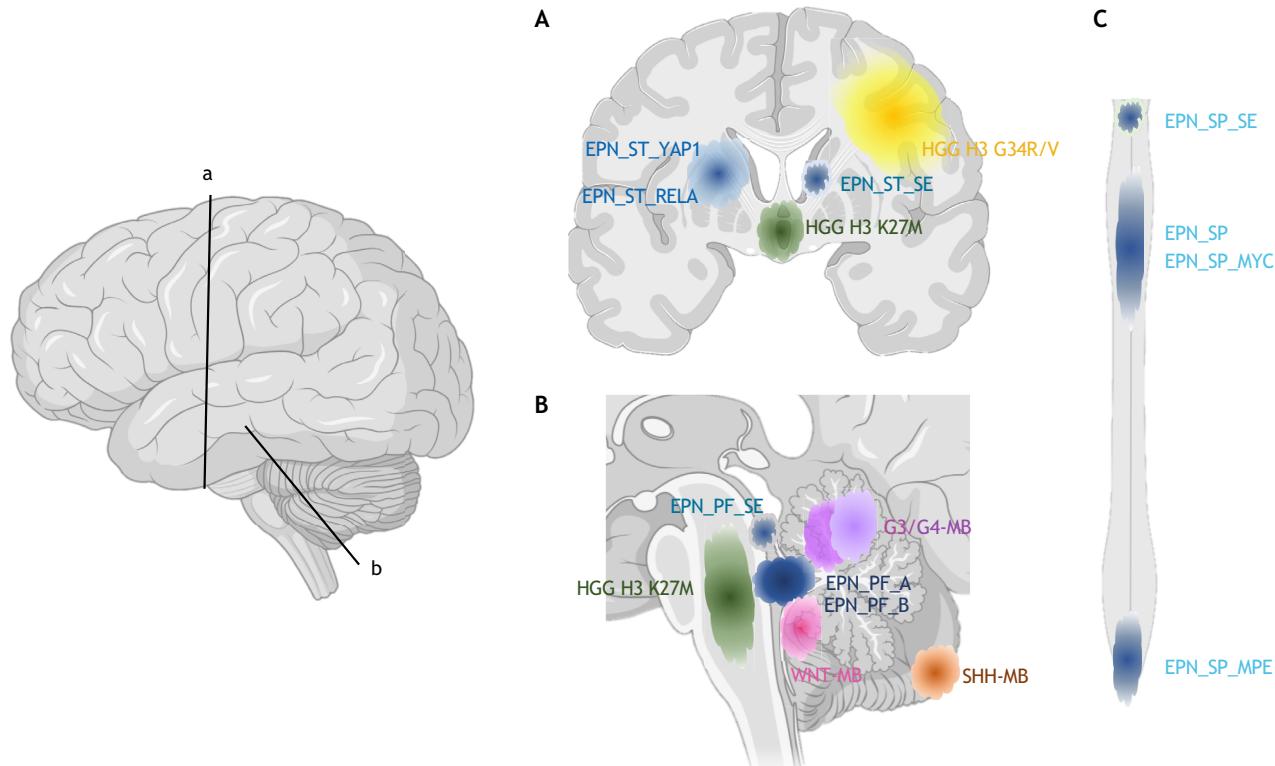


Fig. 1. Genetically defined paediatric brain tumours occur at specific CNS locations. In the forebrain (A), YAP1 fusion (EPN_ST_YAP1) and C11orf95 fusion, e.g. C11orf95-REL A^{FUS} (EPN_ST_REL), ependymomas and subependymoma (EPN_ST_SE) arise within the radial glia lineage in the lateral ventricles, whereas histone mutant gliomas are found at the midline (HGG H3 K27M) and in the hemispheres (HGG H3 G34R/V). In the hindbrain (B), ependymoma A (EPN_PF_A), B (EPN_PF_B) and subependymoma (EPN_PF_SE) as well as certain forms of medulloblastoma (WNT-MB, SHH-MB and G3/G4-MB) arise from various progenitor populations in the cerebellum or in the wall of the 4th ventricle. In contrast, histone mutant gliomas arise in the pons (HGG H3 K27M) and WNT medulloblastoma arise in the dorsal brainstem from mossy fibre precursors. The spinal cord (C) is the site of subependymoma (EPN_SP_SE), as well as spinal (EPN_SP), MYC amplified (EPN_SP_MYC) and myxopapillary ependymomas (EPN_SP_MPE). Figure created with BioRender.com.

have further subclassified the disease into nine molecular subgroups, three each in the forebrain, hindbrain and spine (Ghasemi et al., 2019; Mack et al., 2014; Pajtler et al., 2015; Parker et al., 2014; Witt et al., 2011).

The intersection of developmental and cancer biology is shedding light on how the different subtypes of ependymoma develop and could be better treated. A common emerging theme is the corruption of normal neural lineage development. For example, the most lethal form of hindbrain ependymoma lacks recurrent genetic mutations but represses neural differentiation through extensive methylation of developmentally regulated genes (Mack et al., 2013). Conversely, the deadliest form of forebrain ependymoma is driven by a highly-penetrant C11orf95-REL A translocation (Pajtler et al., 2015; Parker et al., 2014) that appears to drive heterogenous populations of aberrantly differentiating, malignant forebrain lineages (Liu et al., 2020). Thus, ongoing studies are seeking to understand whether aberrant differentiation might be blocked or reversed for therapeutic gain, either by the use of epigenetic modifiers or direct inhibition of the C11orf95-REL A fusion oncogene.

Diffuse intrinsic pontine glioma

DIPG is a highly malignant brainstem tumour of young children, characterized by a unique H3K27M mutation. DIPG shares an active chromatin state with oligodendroglial progenitor cells (OPCs) at key lineage markers, including Olig2, suggesting an origin within this lineage (Nagaraja et al., 2019). In keeping with this observation, introduction of the defining H3K27M mutation into OPCs, but not

more undifferentiated neural progenitor cells, was shown to drive DIPG in mice, suggesting that differentiation into an early oligodendroglial precursor is essential for DIPG tumorigenesis (Larson et al., 2019; Nagaraja et al., 2019). Olig2 $^+$ progenitors have been shown also to act as a cell of origin of glioblastoma (Ligon et al., 2007; Liu et al., 2011), a molecularly unrelated adult malignant brain tumour that occurs throughout the CNS. Thus, Olig2 $^+$ progenitors may be transformed by different oncogenic events to form distinct types of brain tumour. The degree of similarity between these temporally and spatially discrete Olig2 $^+$ progenitors and their relative susceptibility to transformation remains to be determined.

The microenvironment

The brain microenvironment, in particular the perivascular neural stem cell niche, has been implicated extensively in medulloblastoma, ependymoma and glioma development and maintenance (Calabrese et al., 2007; Hambardzumyan et al., 2015; Cheng et al., 2013). Other cell-cell interactions are also emerging as important elements of brain tumour biology. For example, in a manner that mimics the control of OPC proliferation and differentiation by electrical activity (Gibson et al., 2014; Mitew et al., 2018), glutamatergic-stimulated BDNF and neuroigin 3 release from neurons has been shown to promote DIPG cell proliferation (Venkatesh et al., 2015). Cross-talk between neurons and malignant cells has since emerged as a process promoting the proliferation and maintenance of an array of brain tumours as well as carcinomas that have metastasized to the brain, raising the intriguing possibility that such electrical stimulation might prove a novel

Table 1. Key features of most common pediatric brain tumours

Histological diagnosis	Cell of origin	Incidence (per 100,000 population)	5 year survival rate	Typical location	Malignancy grade	Key characteristics
Pilocytic astrocytoma	Unknown	8.2	97%	Cerebellum, brainstem, optic pathway	Predominantly low-grade	Single driver BRAF rearrangement
Medulloblastoma	Cerebellar progenitor cells and mossy fibre precursor cells	5.1	71%	WNT tumours arise outside the cerebellum from mossy fibre precursor cells. The other three subtypes arise from within the cerebellum.	High-grade	WNT, SHH, G3 and G4 molecular subgroups have distinct lineage origins. WNT tumours are uniformly curable. The other three subtypes are less curable.
Ependymoma	Radial glia progenitor cells	2.9	72%	Brain and spinal cord	Low- and high-grade	Forebrain, hindbrain and spinal cord tumours are genetically and molecularly distinct
Diffuse intrinsic pontine glioma	Oligodendroglial progenitor cells	1-2	2%	Brainstem (H3K27M mutant gliomas occur also in other midline structures)	High-grade	Histone H3K27M mutations
Craniopharyngioma	Remnants of craniopharyngeal duct epithelium	1.7	98%	Base of the brain, above the pituitary gland	Low-grade	Papillary (BRAFv600E) and adamantinous (<i>CTNNB1</i> mutations) subtypes
Germ cell tumours	Unclear, possibly ectopic primordial germ cells or pluripotent stem cells	1.5	65%	Midline, around the pituitary gland and the pineal gland	Predominantly high-grade	Germinomas and non-germinomatous tumours
Choroid plexus tumours	Choroid plexus cells and progenitors	1.2	80%	In the ventricles of the brain	Predominantly low-grade	p53, Myc, Notch mutations

Sources: Stiller et al., 2019; Louis, et al., 2017; National Registry of Childhood Tumours/Childhood Cancer Research Group, <http://www.ccrg.ox.ac.uk/datasets/registrations.shtml>.

therapeutic target (Venkatesh et al., 2019; Venkataramani et al., 2019; Zeng et al., 2019).

Perspectives

These studies and the many others that could not be cited in this short opinion piece, provide compelling evidence that brain tumours arise from deregulated developmental processes. Knowledge of the processes that regulate normal development has therefore proved increasingly important to understand brain tumour pathogenesis. We are beginning to see a clear impact of these discoveries on the diagnosis and management of patients with brain tumours. The challenge ahead is now to harness this knowledge to design molecularly driven, risk-stratified clinical trials to eventually improve patient care.

Competing interests

The authors declare no competing or financial interests.

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