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Put away your microscopes: The ependymoma molecular era has begun

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Abstract

Purpose of review—To synthesize, integrate, and comment on recent research developments to our understanding of the molecular basis of ependymoma, and to place this in context with current treatment and research efforts.

Recent findings—Our recent understanding of the histologically defined molecular entity ependymoma has rapidly advanced through genomic, transcriptomic, and epigenomic profiling studies.

Summary—These advancements lay the groundwork for development of future ependymoma biomarkers, models, and therapeutics. Our review discusses these discoveries and their impact on our clinical understanding of this disease. Lastly, we offer insight into clinical and research areas requiring further validation, and open questions remaining in the field.

Keywords

brain tumor; ependymoma; genetics; epigenetics; tumour heterogeneity

INTRODUCTION

Ependymoma is a histologically defined tumor of the central nervous system (CNS) that occurs in children and adults. Ependymomas of childhood arise most commonly within the supratentorial (ST) brain (i.e. cerebral hemispheres) or posterior fossa (PF, i.e. cerebellum and brainstem). Spinal ependymomas occur most often in adulthood. Treatment for ependymoma to this date remains maximal-safe surgical resection followed by conformal

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CONFLICTS OF INTEREST

None

radiation[1]. The effectiveness of chemotherapy for treatment of ependymoma is still highly debated, and continues to be evaluated in numerous ongoing clinical trials (United States - ACNS0831, Europe - SIOP Ependymoma II). There are no targeted therapies in clinical use or being evaluated in multi-center clinical trials for ependymoma. As a result, survival rates have seen limited improvement (~80%) in the last decade, with survivors suffering from the debilitating side effects of treatment-related surgery and radiation.

Historically, histopathologic features have been used to diagnose and risk-stratify ependymoma. However, there has been a failure to develop consistent and reliable criteria to predict ependymoma patient survival, outside of World Health Organization (WHO) Grade I tumors (i.e. subependymoma myxopapillary ependymoma)[2]. Frustration with a lack of consistency with respect to ependymoma histopathologic grading, have motivated clinicians and researchers to leverage unbiased, sensitive, and molecular approaches to both develop reliable prognostic markers of ependymoma, and to decipher the molecular biology of this disease to identify the first set of targeted therapies[3–9].

This review provides a synthesis of recent molecular research developments in the field of ependymoma. We describe the integration and impact of molecular tools and knowledge on our understanding of the biology of ependymoma. We comment upon how these findings may be interpreted with respect to clinical treatment and variables, and propose research areas that require potential future investment.

Ependymoma is comprised of at least nine different subgroups

Through independent analysis of multiple ependymoma cohorts, using transcriptomics, genomics, and epigenomics (termed '-omics') technologies, we now recognize that ependymomas are divided into multiple clinically and biologically distinct subgroups. The most recent large-scale analysis reveals that ependymomas are segregated into at least nine molecular subgroups[9]. ST ependymomas are divided into tumors defined by predominant gene fusions between *C11ORF95-RELA* (72% of ST ependymomas), and less frequently fusions of the *YAP1* oncogene with other gene partners, denoted ST-EPN-RELA and ST-EPN-YAP1 subgroup, respectively [4,9] (Figure 1). PF ependymomas are divided into frequent PF-EPN-A tumors (74% of PF ependymomas) with a poor outcome, and relatively balanced genome, versus PF-EPN-B tumors with increased genomic instability and a favorable outcome[7,8,11] (Figure 1). Within both ST and PF compartments exist WHO Grade I classified subependymomas[2]. Spinal ependymomas frequently harbor loss-of-function *NF2* mutations or deletions, traditionally classified as Grade I or II, and further composed of subependymoma and myxopapillary ependymoma variants[12,13]. These '-omics' profiling studies of ependymoma reveal, in the largest series of cohorts analyzed to date, that ependymomas are comprised of at least 9 molecularly, demographically, and clinically distinct disease entities[9]. They reinforce that, outside of WHO Grade I ependymomas (i.e. subependymomas and myxopapillary ependymoma), histopathologic grading has no prognostic utility. Therefore we recommend that outside of current clinical trials, histopathologic grading of Grade II or III ependymoma should not be used to risk stratify future patients[10] (Figure 1).

Clinical integration of ependymoma subgroups

Molecular profiling of multiple large ependymoma cohorts (namely through Illumina DNA methylation analysis) has allowed for analyses to be made on the impact of molecular subgroup and clinical variables[5,9,11]. A study of four distinct PF ependymoma cohorts revealed that while use radiotherapy is effective in the case of PF-EPN-A tumors that were gross-totally resected, it had limited impact in patients harboring PF-EPN-A ependymoma with a sub-total resection[5]. In the same vein, current clinical trial cohorts that are addressing important questions related to other modalities such as the role of chemotherapy (United States - ACNS0831) need to be analyzed in the context of molecular subgroup. In the case of PF-EPN-B, there potentially exists a population of patients that may be cured with surgery alone, and in the case of recurrence, may be salvaged with radiotherapy[5]. This raises a possibility of future clinical efforts to study therapy de-escalation for PF-EPN-B patients[10]. Similar molecular and multi-cohort analysis of ST ependymoma is needed to validate the incidence of *C11ORF95-RELA* and *YAP1* fused tumors in other ependymoma cohorts, and their correlation with survival and other clinical parameters[10]. In contrast to ST-EPN-RELA tumors, which have been shown to have a poor outcome, ST-EPN-YAP1 tumors perform favorably, thus suggesting potentially distinct treatment modalities for this distinct patient population in the future. We therefore recommend that future ependymoma clinical trials should stratify patients by their molecular features, or at very minimum collect frozen tissue for future molecular diagnostics[10].

Frequent fusion oncoproteins define supratentorial ependymoma

72% of ST ependymomas harbor a gene fusion between *C11ORF95* and *RELA*, now recognized by WHO as a distinct clinical entity[2,4]. This event leads to sequestration of the *C11ORF95-RELA* fusion protein within the nucleus causing aberrant NF-κB activity[4]. Viral over-expression of the *C11ORF95-RELA* fusion protein in murine embryonic day 14.5 radial glial cells (candidate cell of origin of ependymoma) is capable of cellular transformation and tumor initiation, when transduced cells are implanted in immunodeficient mice[4]. Although *C11ORF95-RELA* is the most commonly observed fusion, other fusion events have been observed[4]. Recurrent fusion of *YAP1* with other fusion partners is thought to induce a distinct subgroup of ST ependymoma, labeled ST-EPN-YAP1 [9]. Unlike ST-EPN-RELA tumors, which have been reported to have a poor survival, ST-EPN-YAP1 tumors carry a favorable prognosis and respond well to current treatments[9]. There remain several important questions to be validated, that similar to PF ependymoma, would benefit from an expanded molecular based analysis of multiple ST ependymoma cohorts. For example, the incidence of these fusion events in ST ependymoma needs to be independently validated. Are ST-EPN-YAP1 fused tumors substantially over-represented from other non-*C11ORF95-RELA* fusion events? In other cohorts, do *YAP1* fused ependymomas carry a favorable prognosis? More broadly, do all ST ependymomas carry a gene fusion? It will be important that current and future ST ependymoma clinical trial studies examine the incidence, and clinical associations with clinical parameters of onco-fusion protein events[10]. While Illumina DNA methylation provides an indirect (yet highly reliable) measure of molecular subgroup associated with a particular fusion, break apart fluorescence in situ hybridization can be used to identify and verify samples harboring the *C11ORF95-RELA* fusion. RNA-seq also provides an approach to identify *C11ORF95-*

RELA fusions and provides a discovery method to identify novel or less obvious fusion events. Therapeutically targeting these fusion oncogenic events is currently a challenge as this class of transcriptional machinery proteins (i.e. Transcription factors and regulators) has been challenging in the past to target with small molecules. There may be potential in evaluation of NF-κB or YAP1 inhibitors in pre-clinical models where available[14,15]. An important direction moving forward will be to determine if these fusion proteins reveal potential druggable binding partners and synthetic lethal cancer cell dependencies[16,17].

Global epigenomic rewiring defines posterior fossa ependymoma

PF ependymoma are divided into two principle molecular subgroups, PF-EPN-A and PF-EPN-B. PF-EPN-B tumors arise in older children through to adulthood, carry a favorable prognosis, and also demonstrate widespread chromosomal aneuploidy[8]. This is in direct contrast to the most frequent PF-EPN-A subgroup (74% of PF cases), which despite in-depth genomic characterization, has yet to reveal a highly recurrent focal driver alteration[10,18]. Despite lacking a clear genetic driver mutation, PF-EPN-A tumors demonstrate widespread epigenomic alterations in the form of DNA CpG island hypermethylation and global DNA hypomethylation, a phenotype well described in many solid cancers[10,18–20]. Furthermore, PF-EPN-A tumors demonstrate global H3K27me3 loss, a histone modification important for regulating bivalent gene expression and maintaining cell identity[21,22]. Gene targets of DNA and H3K27 hypermethylation overlap significantly with patterns of DNA and histone H3K27 methylation seen in embryonic stem cells. Perhaps a necessary component of neoplastic transformation of ependymoma cells involves acquisition of features found in the embryonic stem cell state. Interestingly, diffuse intrinsic pontine gliomas (DIPGs) that carry recurrent K27M mutations exhibit similar patterns of global H3K27me3 and DNA methylation loss, suggesting potentially convergent mechanisms of neoplastic transformation and/or similar cell types or states that give rise to these distinct brain tumor entities[23,24]. Although very rare, a small subset of PF-EPN-A ependymomas harbor K27M mutations, raising the question as to what is the cause of global DNA and H3K27me3 loss in non-histone mutated ependymoma[25]. This also raises the opportunity for potential shared therapeutic paradigms to exploit dysregulated epigenomes. As seen in ependymoma and DIPG, the residual H3K27me3 in tumors is important for tumor cell maintenance, because inhibition with EZH2 inhibitors is sufficient to block tumor cell growth[11,18,19,26,27]. Research efforts in the future may benefit from exploring the potential for exploiting tumors that demonstrate global H3K27me3 loss for potential synthetic lethal pathways[16,17].

Models desperately needed

Understanding the genetic basis of ependymoma has led to the development of *ex vivo* models through over-expression of the C11ORF95-RELA fusion protein, and implantation of transduced radial glia into immunodeficient mice[3,6,28]. This has allowed for the mechanistic dissection of the biology of C11ORF95-RELA fusion protein in initiating and maintaining ependymoma tumorigenesis in mouse models. These mouse isogeneic models offer opportunities to identify ST-EPN-RELA cell dependencies through mechanistic study, and genetic and chemical screens. They also provide a foundation for development of transgenic ependymoma models, which would be useful for mapping the cellular origins of

the disease. Still widely lacking is the availability of human patient derived models. In the case of *C11ORF95-RELA* tumors, the model EP1-NS harbors the *RELA* fusion and shares similar transcriptional and DNA methylation signatures with human primary ST-EPN-RELA tumors (data unpublished)[29]. Given the number of ependymoma subgroups, additional models are desperately needed for pre-clinical therapeutic development. This is especially the case for PF-EPN-A ependymoma where primary cultures can be maintained for a few passages before they senescence or begin to exhibit patterns of genetic and epigenetic drift. Given the rarity of these tumors, collaborative efforts are essential to establishing, sharing, and characterizing new ependymoma models in order for biological advancements to proceed[10].

Conclusion: The future of '-omics' to study ependymoma

'-omics' based discovery approaches identified the main driver of ST ependymoma. Can additional applications such as epigenomics, proteomics, single cell analysis, and metabolomics reveal other oncogenic drivers, and offer further insight into the mechanisms of ependymoma-genesis? Such analysis may proof useful in the case of PF-EPN-A and PF-EPN-B ependymomas where frequent drivers are unknown. For example, the repressive landscape has been defined through histone methylation mapping, but what about other epigenetic modifications in particular active epigenomic marks, such as H3K27 acetylation? Could these actively transcribed domains reveal recurrent regulatory programs that lead to oncogenic activation as reported in other brain tumors?[30] Will metabolic approaches performed in primary tumors help us determine the optimal conditions for primary cell culture, such that more models are established, and platforms can be developed for therapeutic screening? Have we missed cryptic lesions or mutations that might be revealed with advanced genomic sequencing? Have we underestimated the full degree of heterogeneity within subgroups of ependymoma, and that these tumors - like medulloblastoma - are composed of many more subtypes?[31,32] These questions may be answered readily with continued partnerships between researchers and clinicians, working towards international collaboration and shared access to samples, models, and data.

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KEYPOINTS

1. Outside of clinical trials histopathologic grading II/III of ependymoma is not useful
2. Ependymoma is composed of at least nine different diseases
3. Frequent gene fusions define supratentorial ependymoma, namely *C11ORF95-RELA*
4. Global epigenomic rewiring defines posterior fossa ependymoma
5. '-omics' based tumor characterization will continue to unravel the molecular basis of ependymoma and its subgroups

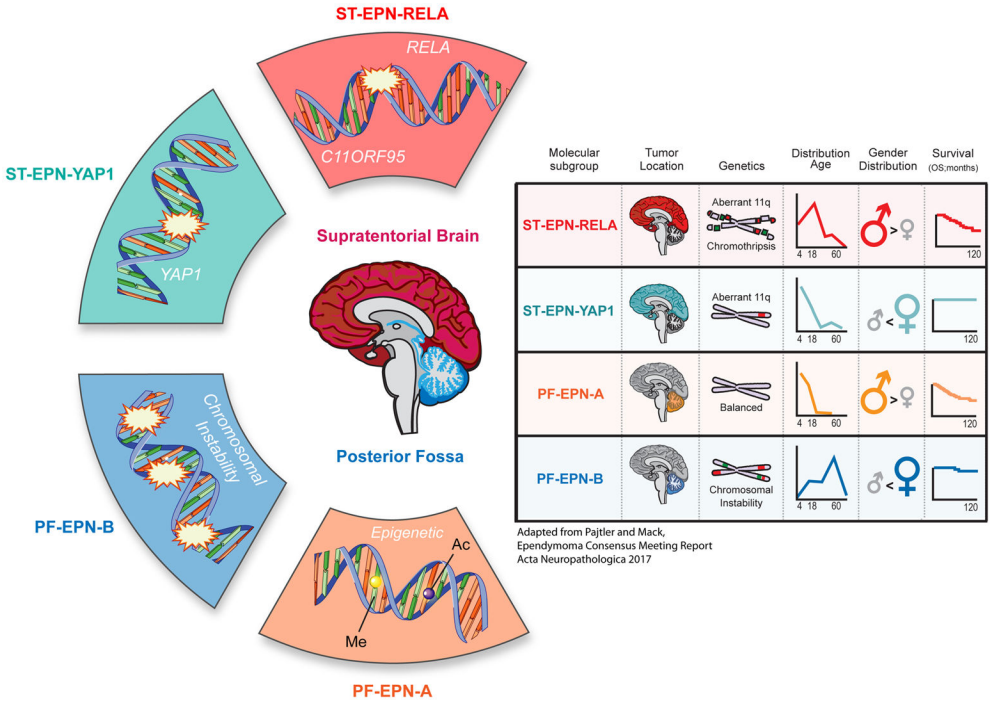

Figure 1.

Summary of intracranial ependymoma subgroups and recommendations for future ependymoma clinical trials. Adapted from the Ependymoma Consensus Meeting manuscript[10].