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Molecular pathology of adamantinomatous craniopharyngioma: review and opportunities for practice

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Since the first identification of *CTNNB1* mutations in adamantinomatous craniopharyngioma (ACP), much has been learned about the molecular pathways and processes that are disrupted in ACP pathogenesis. To date this understanding has not translated into tangible patient benefit.

The recent development of novel techniques and a range of preclinical models now provides an opportunity to begin to support treatment decisions and develop new therapeutics based on molecular pathology.

In this review the authors summarize many of the key findings and pathways implicated in ACP pathogenesis and discuss the challenges that need to be tackled to translate these basic findings for the benefit of patients.

Key Words adamantinomatous craniopharyngioma; molecular therapeutics; targeted therapies

Abbreviations ACP = adamantinomatous craniopharyngioma; cfDNA = cell-free DNA; EGFR = epidermal growth factor receptor; PCP = papillary craniopharyngioma.

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THE last 2 decades have seen an explosion in the understanding of tumor biology, in a large part attributable to advances in technology facilitating high throughput analyses of samples. Such advances in understanding have resulted in some significant developments in diagnosis, risk stratification, and treatments for some, but not all, tumors.

The identification of BRAF V600E mutations in papillary craniopharyngioma (PCP) has resulted in exciting novel therapies for patients with this form of craniopharyngioma.[6,8,9] In contrast, for adamantinomatous craniopharyngioma (ACP), while mutations in the gene *CTNNB1* have been identified in the majority of cases, no such "magic bullet" treatments have been translated into the clinic yet. In this review we summarize recent advances in the understanding of ACP pathology and discuss how this might impact practice in the future. More detailed reviews of the histopathology of ACP, specific pathways, and the lessons learnt from mouse models may be found elsewhere.[30,35,36,41]

Opportunities for Practice

ACP is a clinically heterogeneous disease. At presentation tumors may be variably solid to cystic and variably invasive and destructive of neighboring structures.[39] Disease course can vary, with some tumors remaining indolent despite incomplete resection with or without radiotherapy, whereas others may rapidly recur despite apparent gross-total resections and radiotherapy.[39] A better understanding of the molecular pathology of these tumors will provide novel insights into the underlying mechanisms responsible for this heterogeneity in clinical course. In addition, such understanding will form the first steps toward the generation of novel predictive tools that could allow us to tailor therapies to the particular tumor biology as summarized in Table 1. This precision medicine concept has not benefited ACP patients so far, but it is beginning to have impact for other tumors and cancers, particularly in neuro-oncology, such as with medulloblastoma.[52]

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Currently, for most ACP patients, therapies are limited to surgery and radiotherapy, both of which carry significant risks of further morbidity and are associated with poor quality of life.[39] While intracystic therapies have been used and show some promise in the management of cysts, so far targeted therapies are not used in ACP.[7] A better characterization of the pathways underlying tumor formation offers the potential to identify novel, rationally designed, targeted therapies for the benefit of the patients.

In addition, while many patients are "cured" of their tumor, long-term consequences of the tumor, such as hypothalamic obesity, can have profound effects on both survival and quality of life.[39] Although outside the scope of this article, understanding the biology of these may also lead to patient benefit.[61]

Methodologies Used to Understand the Molecular Pathology of ACP

A range of methodologies have been applied to the study of ACP pathogenesis, usually using both archived frozen and paraffin-embedded samples. Approaches can roughly be divided into broad "-omics" analyses (e.g., exome sequencing and expression microarray) or targeted assays of small numbers of genes/targets. To model the disease, fresh surgically obtained ACP tissue has been used in vitro to isolate primary cell cultures, and recently, a new orthotopic xenograft model has been described.[12,22,50] Two genetically engineered models, expressing a functionally equivalent form of oncogenic β-catenin to that identified in human ACP, have given valuable insights into the processes underling tumorigenesis.[3,4,15] It is likely that to translate any new findings into novel therapeutic opportunities, a multidisciplinary approach combining several or all of these existing methodologies and perhaps new assays (e.g., circulating cell-free DNA (cfDNA) and proteomics) will be required.

Several emerging methodologies present great opportunities for translation. The detection of BRAF V600E mutations in the blood of patients with PCP highlights the potential of identifying *CTNNB1* mutations in cfDNA of ACP patients, therefore facilitating less invasive diagnostic testing, residual disease assessment, and risk stratification.[8] Similarly, highlighting the potential for novel approaches for disease monitoring, it has been reported that urinary levels of matrix metalloproteinases were raised in a girl with recurrent ACP and subsequently became normalized following resection of the tumor.[48] Detailed proteomic analyses of cystic fluid, or even lipidomic and metabolomics analyses, could lead to the characterization of a profile unique for ACP, which could help both diagnosis and treatment response.[40] To maximize the opportunities of these approaches large cohorts of samples with associated well annotated clinical data will be required.

Genetic Changes in ACP

Activating mutations of the WNT pathway gene *CTNNB1* (encoding β-catenin) have been identified by several groups in ACP over the last 10 years and are increasingly recognized to occur in the majority, if not all ACPs.[10,29,45] Immunostaining for β-catenin and/or sequencing of *CTNNB1* in surgical samples is now used in practice in many centers for diagnostic purposes. These *CTNNB1* mutations are predicted to lead to enhanced half-life of β-catenin resulting in its nucleo-cytoplasmic accumulation in the cells bearing such mutations. The pattern of β-catenin expression, however, is unusual in ACP because nucleo-cytoplasmic accumulation is limited to a proportion of the tumor cells, often only those cells within the

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epithelial whorls/nests, which are sometimes referred to as "clusters."[10,29] The reasons for this heterogeneity in β-catenin protein localization and expression are not fully understood.

Whether mutations in other genes contribute to tumor formation or tumor behavior (e.g., infiltrative capacity) is not known. The first exome sequences were published in 2012 by Brastianios et al., who by sequencing 12 ACP samples and matched germline DNA found *CTNNB1* mutations to be the only recurrent mutations. Mutations in other cancer-related genes (including transcriptional regulators, epigenetic regulators, and DNA repair and cell adhesion genes) were also identified in individual cases, but were not recurrent between patients in this small series.[9] Consistent with findings for other pediatric tumors, Brastianos et al. found the overall mutation frequency to be relatively low in human ACP.[9] As more ACP tumors are sequenced, the presence of other recurrent mutations, or recurrently disrupted mutated pathways may become more apparent in the future.

While cases of ACP tumors bearing mutations in both *CTNNB1* and *BRAF* have been reported, this seems unlikely to be a common phenomenon.[23,31]

With respect to genomic copy number alterations, previous studies using G banding or comparative genomic hybridization have given variable, often controversial, results. While the majority showed normal karyotype cases with copy number variants were described in some cohorts.[23,44,58] Clearly, a better molecular characterization of more ACP tumors is required to determine and refine the mutational landscape of these tumors.

Gene Expression and Methylation Analyses of ACP

The first genome-wide transcriptome cohort study using expression arrays of 15 ACPs was published during 2015.[19] In addition to highlighting previously identified pathways (e.g., the sonic hedgehog [SHH] and epidermal growth factor receptor [EGFR] signaling pathways), this analysis identified a number of other potential therapeutic targets (including MMP12, IL2B, LCK and EphA2) using the Ingenuity Pathway Analysis (IPA, Quiagen) knowledge-based program.[3,19,22] Gene Ontology analysis of genes differentially expressed in ACP revealed genes implicated in odontogenesis, epidermis genes (e.g., keratins), and cell adhesion genes.[19]

An additional 18 ACP samples underwent expression array analysis and were compared with 10 PCP samples by Holsken et al. in 2016.[23] This study also highlighted the activation of the WNT and SHH pathway in ACP. In this paper, the methylation profiles of 25 ACPs and 18 PCPs were assessed, revealing distinct patterns between tumor types. Specifically, ACP was found to show hypomethylation of the WNT pathway gene *AXIN2* and the SHH pathway genes *GLI2* and *PTCH1* when compared with PCP. The limited sample size in these 2 independent studies did not allow for further subclassification of ACP into consistent subgroups as has been seen in other tumor types.

Specific Genes/Pathways Upregulated or Activated in ACP

Several molecular pathways have been implicated in ACP pathogenesis, the best characterized of which are summarized in Table 2.[1,3,16,18,19,22,26,32,34,38,40,43,46,50,60] The complex tissue architecture of ACPs, with a range of cell types (e.g., palisading epithelium, stellate reticulum, clusters, reactive glial tissue, and inflammatory cells), has posed a particular challenge. It is important to interpret the molecular data in the context of the appropriate cell types within the tumor and surrounding reactive tissue. Moreover, many of these pathways—

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e.g., WNT, SHH, BMP, and FGFs—play important roles not only in tumorigenesis, but also in organ homeostasis of several tissues, posing challenges for safe therapeutic targeting. In other words, we believe that it is important not only to characterize the molecular profiles of human ACP, but also to understand the role of the dysregulated pathways in specific cell compartments.

Molecular Biology of β-Catenin–Accumulating Cell Clusters

The mouse models of ACP have highlighted the potential roles of β-catenin–accumulating clusters in driving ACP tumorigenesis.[3,4,15] This, coupled with their stem cell–like markers, e.g., CD44, SOX2, have made these clusters of particular interest when studying the signaling pathways underlying the development and progression of ACP.[4,24] Indeed activation of *CTNNB1* in adult pituitary SOX2 positive stem cells alone leads to tumors resembling ACP.[4]

Studies have shown that these clusters may act as signaling centers expressing high levels of secreted factors such as SHH, FGFs, BMPs and WNTs, with paracrine actions on neighboring cells.[3,4] As previously mentioned, many of these factors have been described to be up-regulated in human ACP, specifically in the clusters. The inducible ($Sox2^{CreERT2/+}$, $Ctnnb1^{lox(ex3)/+}$) mouse model of ACP suggests a possible non-cell autonomous mechanism of tumorigenesis, though the extent at which this model applies to human tumors requires further investigation.[4]

Clusters have also been suggested to be involved in tissue invasion. Both high-resolution 3D imaging of human tumors and analysis of human tumors in a xenograft mouse model have identified clusters at the leading edge of tumor invasion.[5,50] Knockdown of *CTNNB1* or the β-catenin target *FASCIN-1* reduced migration and wound healing by primary ACP cells in vitro.[21] Activation of the cell surface receptor epidermal growth factor receptor (EGFR) has also been shown in human tumors, and its inhibition reduced migration of ACP cells in an in vitro assay.[22] Other factors suggested to have roles in the invasion of ACP include matrix metalloproteinases, E-cadherin, vimentin, and claudin-1.[42,49] However, so far no studies have assessed the relevance of these pathways and their inhibition in in vivo models of human ACP.

Molecular Pathology of Tumor Cysts

For many patients, it is the cystic component rather than the solid tumor that poses a significant clinical challenge. Cyst fluid has a so-called “motor oil” appearance and is rich in cholesterol, with variable necrotic and inflammatory debris.[59] Several studies have begun to investigate the molecular biology underlying cyst formation, as existing intracystic therapies have been largely empirical in their mechanism of action.[7]

It has long been recognized that leakage of cystic fluid can lead to local inflammation, and this has been modeled by injection of cystic fluid into the brain of rats, which induces an inflammatory response and an increase in GFAP expression.[47,53,54] Expression of a number of inflammatory mediators, such as IL6, IL1A, TNF, and α-defensins 1–3, has been identified in cystic fluid, generating interest in the use of immunomodulators for the treatment of cysts.[34,38,40]

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The histopathological similarities between ACP and odontogenesis and frequently cystic odontogenic tumors such as ameloblastoma and calcifying odontogenic cyst has also been recognized, but the molecular biology of these similarities / links remains relatively underexplored.[59]

Molecular Biology of Tumor-Associated Angiogenesis

Several studies have investigated the microvascular densities in ACP and the expression of a range of pro-angiogenic (e.g., vascular endothelial growth factor, VEGF) and antiangiogeneic (e.g., endostatin) mediators with conflicting results with regard to association with recurrence risk.[2,13,51,55–57] One functional study using a corneal angiogenesis assay revealed that recurrent ACP samples had a significantly higher angiogenic potential than nonrecurrent ACP, but less than glioblastoma multiforme or arteriovenous malformations.[51] Imatinib-loaded microspheres reduced neovascularization in this model, but the use of this or other antiangiogenic approaches in patients has not been reported in the literature.[28]

Molecular Biology of Tumor Recurrence

Primary treatment of ACP aims to minimize the risk of recurrence with maximum preservation of the hypothalamic pituitary axis and quality of life. Understanding why some patients relapse while others do not could help in tailoring the approach to management. Similarly, current treatments for relapse are often unsatisfactory, leading to further surgery, increased morbidity, and reduced quality of life. It is in these cases of persistent recurrences that novel therapies could perhaps be most rapidly translated.

Many studies have compared the expression of specific molecules, including many described in Table 2, in samples of recurrent ACP with or without comparison with nonrecurrent ACP. One study performed expression microarray analysis in 2 pairs of matched primary and relapse samples and identified 20 genes, including *CXCR4* and *CXCL12*, that were upregulated in recurrent samples.[17] The authors then went on to assess these 2 markers in a larger retrospective cohort of 45 patients and found those with higher levels to have a higher risk of relapse. In another study, Lefranc et al. found that recurrent ACP expresses higher levels of RARγ□□□□ cathepsin-K and lower levels of galectin-3, RARβ, and cathepsin-D than nonrecurrent ACP.[33] A review in 2013 found variable associations of recurrence with proliferation markers and TP53 expression.[41]

These individual studies on recurrence have generally used univariate analyses on relatively low sample numbers of archival specimens limiting the generalizability of their findings and likely contributing to their lack of reproducibility or consistency when repeated.

Malignant transformation of ACP is extremely uncommon. In the limited molecular studies to date, increased expression of proliferation markers and TP53 have been observed in malignantly transformed specimens as well as in some rapidly recurring tumors.[25,41] While TP53 expression appears to be rare in nontransformed ACP, its related family member TP63 is widely expressed, particularly the deltaNp63 isoform[11,14,37]

Translating the Therapeutic Opportunities and Challenges Ahead

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The limited nature of current treatment strategies (surgery and radiotherapy) and absence of prognostic biomarkers (e.g., imaging or molecular) make the management of ACP very challenging. Further molecular characterization is needed, but how to translate these basic findings into the clinic poses significant challenges.

Confounding factors, such as type of resection and radiotherapy, must be considered when correlating molecular features with outcome, requiring matching of clinical data with biological specimens. Similarly, tumor samples vary both between and within patients with respect to overall tumor content, presence of different cell types, overall activation of the WNT pathway, and extent of the cystic component, just to mention a few factors. For instance, some tumor samples have extensive wet keratin or are mostly cystic or present large areas of β-catenin–accumulating cell clusters with activation of the WNT pathway, while others show little wet keratin or minimal accumulation of β-catenin and WNT pathway activation. Such factors must be taken into account, but there is a risk that by introducing a bias—for example, including only samples with "high" tumor content—future studies may fail to represent the true breadth of the human disease.

The neurosurgery community is increasingly adopting a safer and more conservative surgical approach to ACP, and so tumor specimens may become more rare as well as smaller. Therefore, prioritization between clinical diagnostic use and varying research demands (e.g., for nucleic acid extraction, immunohistochemistry, primary cell cultures, or xenografts) will need to be carefully balanced. Historically, many analyses have been conducted on archival specimens; however, some novel approaches, such as cfDNA, will require the collection of samples (e.g., plasma, cerebrospinal fluid, and even urine) from patients.

The rarity of patients and samples will require collaborative cross-center projects with adequate collection across the centers, an important challenge as some are likely to see very few cases per year. Many of these challenges also exist for many other tumor types, and integrating approaches with those for other tumor types (e.g., brain tumors) will facilitate the collection of biological and clinical data.

Now that many pathways and potential targets have been identified in human ACP we need to move forward to the next level and test their biological functions in the context of preclinical models, primary cell cultures, xenografts, and genetically engineered mouse models. These are suitable tools to investigate potential new therapies, but one needs to be aware of their limitations as well as their strengths, as they are likely to model specific aspects of the human disease. Well-designed preclinical trials incorporating some of all of the current treatment modalities (e.g., surgery and radiotherapy) may increase the chance of predicting the effect of these new antitumor agents in human patients with ACP. While resection of pituitary tumors in genetically modified mice may not be possible, the use of stereotactic radiotherapy in mice offers the chance to study tumor response and more accurately reproduce a human tumor's treatment and disease course. Such an approach has been developed in Erlangen for the treatment of mice xenografted with human tumor tissue through adaptation of a clinical linear accelerator.[20]

There are existing targeted therapeutics approved for use in other tumor types for some of the pathways potentially implicated in ACP pathogenesis. While these are immediately appealing for rapid translation and use in ACP, it must be noted that unanticipated effects can be seen. The experience of use of SHH pathway inhibitors in pancreatic cancer, or BRAF inhibitors in *BRAF*-fusion gene–positive low-grade gliomas highlights this best, as treatment was found to promote rather than inhibit tumor growth.[27,32,43]

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Conclusions

Previously overshadowed by other brain tumor types, the molecular biology of ACP is an increasingly exciting field with a range of "-omic" datasets being published or in progress and a diverse range of experimental models available for both understanding the functional impact of findings and the testing of novel therapeutics.

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