Transcriptomic and Genomic Analyses of Human Craniopharyngioma

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Abstract Recent studies of the genome and transcriptome of human craniopharyngioma have contributed significant insights into our understanding of these tumors. Genomic studies of adamantinomatous craniopharyngioma (ACP) have revealed mutations in the *CTNNB1* gene, resulting in nuclear and cytoplasmic accumulation of β-catenin protein. Papillary craniopharyngioma (PCP), however, is characterised by the BRAF V600E mutation, which suggests novel therapeutic strategies. These mutations appear to be mutually exclusive, implying that ACP and PCP are distinct tumor types. Studies of the craniopharyngioma transcriptome, while few, have raised additional therapeutic possibilities, such as potentially targeting matrix metallopeptidases. While a phase II clinical trial for targeted therapy in PCP is forthcoming, additional studies and confirmation of the current preliminary findings are required for advancing novel therapies for ACP.

Keywords Craniopharyngioma genomics • Craniopharyngioma transcriptomics • CTNNB1 • β-catenin • WNT pathway • BRAF

Introduction

Historically, therapy for human craniopharyngioma (CP) has been limited by an incomplete understanding of the biology of these highly morbid lesions. As described in previous chapters, there have been considerable advances in our knowledge over the last decade and a half, based on improved laboratory techniques and studies of novel animal models. While progress has been somewhat slower than that

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seen with some other pediatric and adult brain tumors, such as medulloblastoma [1], ependymoma [2], diffuse lower grade gliomas [3], and glioblastoma [4] analyses of the CP genome and transcriptome have provided considerable insight into the origins of this tumor and the drivers of growth. Further development of these lines of research will guide the development of novel therapies against CP.

This chapter summarises the current state of knowledge regarding the genome and transcriptome of both adamantinomatous (ACP) and papillary (PCP) craniopharyngioma. As the data suggest that these tumors are genetically distinct entities, they are presented as such. With regard to each tumor type, we briefly discuss the most well-established pathways that contribute to tumorigenesis and growth.

Adamantinomatous Craniopharyngioma

β-Catenin and the WNT/Wingless Pathway

The WNT/wingless pathway is well-established in oncogenesis and harbors the only known recurrent genome level aberration in ACP.

In the normal physiological state, Wnt/wingless signaling is involved in organogenesis and adult stem cell maintenance [5, 6]. Among the key members of the canonical WNT signaling pathway is β-catenin [7, 8]. This protein plays an integral role in development, cellular proliferation, differentiation, and cell migration [7, 9–11]. The WNT pathway is maintained in its default off state by a β-catenin destruction complex that restrains β-catenin within the cytosol and facilitates its ubiquitination and proteasomal degradation [12]. Exogenous Wnt signaling transitions this pathway away from the off state [12]. Nuclear β-catenin, therefore, is a hallmark characteristic of active canonical Wnt signaling [5].

In the inactive state, β-catenin is a submembranous component of the cadherin complex [13, 14]. It forms adherens junctions at the cell membrane, where it interacts with E-cadherin and A-cadherin to tether the actin cytoskeleton to the membrane. There it helps preserve cytoskeletal architecture and is involved in polarity and intercellular connectivity [6, 12, 13, 15]. Typically, β-catenin in the cytoplasm is bound and inactivated by a destruction complex [13]. This destruction complex is likely controlled by Axin, a tumor suppressor protein that serves as a multimeric scaffolding protein [12]. Axin recruits and binds to adenomatosis polyposis coli (APC), a tumor suppressor protein, as well as GSK3beta, casein kinase 1α, and protein phosphatase 2A (PP2A) [9, 12, 13]. APC is phosphorylated by these kinases, resulting in recruitment of β-catenin to the complex [12, 13]. These kinases tag β-catenin for degradation through phosphorylation of the serine (S33, S37, S45) or threonine (T41) residues of exon 3 on the *CTNNB1* gene [12, 13]. This phosphorylation pattern is recognised by a component of E3 ubiquitin ligase, b-TrCP, which ubiquitinates β-catenin, thereby targeting it for proteasome-mediated degradation [9, 12]. When β-catenin is phosphorylated within the multiprotein degradation complex, Wnt signaling is inactive [9].

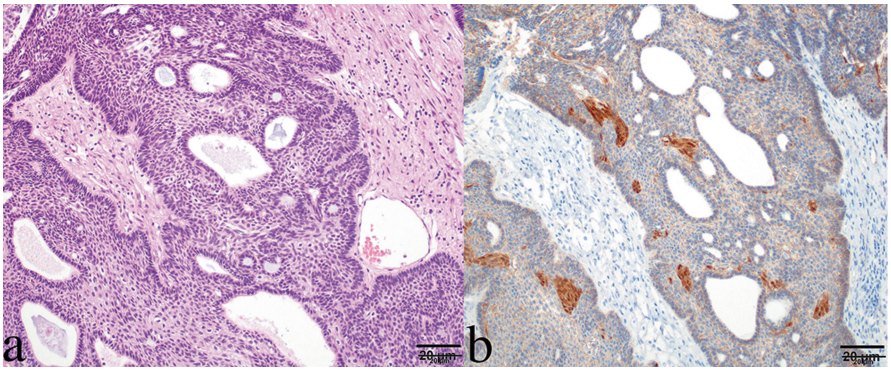

Fig. 1 Histological specimens of adamantinomatous craniopharyngioma demonstrating epithelial regions admixed with microcysts and a reactive glial surround: (**a**) Haematoxylin and eosin stain; (**b**) Immunohistochemistry for β-catenin demonstrates nuclear and cytoplasmic staining in the epithelial cells without uptake in the glial or cystic regions of the tissue

The Wnt protein family includes approximately 20 different proteins that bind to the Frizzled (Fz) family of receptors. When these Wnt proteins bind the highly conserved, cysteine rich extracellular domains of Fz receptors, the Wnt pathway is activated [12] resulting in an intracellular signaling cascade that promotes dimerisation of Fz with LRP5/6 [10, 12]. The Fz/LRP5/6 dimer can bind to Axin, GSK3β, and CK1, which facilitates their accumulation at the cell membrane, preventing them from joining the β-catenin destruction complex [9, 10, 12, 13, 16]. In the absence of the destruction complex, β-catenin protein accumulates and ultimately translocates to the nucleus, where it activates tcf/let transcription factors. This allows transcription of β-catenin target genes and stimulation of cellular proliferation and other Wnt regulated cellular processes [9, 10, 12, 13, 16, 17].

Neoplastic cells with elevated β-catenin levels and activated target genes demonstrate increased migratory capacity and invasiveness [13]. In ACP, this is demonstrated by β-catenin accumulation within cell clusters that are localised at invasive protrusions of tumor into normal brain [13] [Fig. 1]. These processes may be facilitated by *fascin-1*(fascin), a β-catenin tcf signaling target gene, which is involved in the migration mechanism and reorganisation of the actin cytoskeleton, as needed for cellular motility [13, 18]. The promoter region for fascin contains a TCF-binding region, which allows β-catenin to regulate fascin expression [12]. Fascin, an actin-bundling protein, functions by cross-linking F-actin, which is critical for filopodia formation and rigidity, and is frequently seen in migrating cells [12, 13]. Many transformed cell types demonstrate increased fascin expression. This is particularly notable in colorectal cancer, where fascin is found at the invasive edges [13]. Fascin is also overexpressed in ACP cell clusters that have nuclear accumulation of β-catenin [18]. Fascin, in association with β-catenin, is felt to promote migration and invasion of ACP cells. β-catenin can bind fascin by its armadillo repeat sequence which promotes reallocation of β-catenin, changes cell adhesion properties, and reduces β-catenin destruction [13]. Armadillo repeat units 10–12 are integral to

translocation of β-catenin via the passive nuclear-pore-complex [15]. This armadillo sequence of β-catenin is also involved in the E-cadherin and APC interactions [13]. β-catenin accumulation can reduce E-cadherin expression, which reduces cell adhesion and likely leads to cells that are more motile and, as a result, more invasive [13]. Inhibition of fascin or β-catenin expression has been shown to decrease the migratory capacity of ACP tumor cells in culture [13]. Other binding products for the armadillo repeat sequences include TCP-family transcription factors, Axin2, and APC [15].

Increased expression and/or activation of β-catenin likely leads to active expression of multiple target genes. These genes include *Lef1*, *Axin1*, *c-myc*, and CyclinD1, which is a major regulator of cell-cycle progression to the proliferative stages [5, 10, 11, 16]. *Axin2*, a well-recognised inhibitor, and *BMP4*, which plays a critical role in tooth development and increases cell proliferation in conjunction with β-catenin accumulation, are also target genes with increased expression as a result of increased Wnt signaling [9, 12, 16]. Both Axin2 and BMP4 were shown to co-localise to the nucleus with β-catenin with increased mRNA levels [9, 12, 13, 15]. Lef1, an enamel protein, expression is activated by BMP4 [15, 16].

ACP Genome Analyses

CTNNB1 Mutation

Exon 3 of the *CTNNB1* gene (β-catenin) encodes a degradation targeting motif. Mutation may confer resistance of the protein to the usual destruction complex [11, 16] and manifest through nuclear accumulation of β-catenin [5, 7, 10, 11, 19]. The first descriptions of this genome level aberration in ACP demonstrated *CTNNB1* mutations in 69–100% [6, 16, 20] of ACP specimens and the absence of such mutations in PCP and other parasellar tumors [6, 16]. Using massively parallel sequencing of 12 specimens of ACP, followed by targeted genotyping in an additional 53 specimens *CTNNB1* mutation, were identified in 95% (11/12 and 51/53) of specimens [21]. *CTNNB1* mutations were absent in PCP. Other groups have identified *CTNNB1* mutations in approximately 70–80% of ACPs [12, 16, 19, 22]. Although the source of thus variation remains unknown, potential explanations could include intratumoral heterogeneity, sampling error, or even the existence of multiple subtypes of ACP.

As described above, the majority of *CTNNB1* mutations in ACP are upregulating and involve phosphorylation of serine or threonine sites encoded by exon 3, which ultimately encode the degradation targeting box of β-catenin, which corresponds to the GSK3β binding domain [5, 7, 9, 11–13, 19, 20]. Mutations of *CTNNB1* have been identified at a number of different codons [9, 15, 16]. These include codon 32, which is adjacent to the phosphorylation site of GSK3β, as well as codons 33, 37, and 41, which affect the serine and threonine residues that are targeted by GSK3β [6, 9, 14, 15, 19].

The presence of the *CTNNB1* mutation in ACP may offer insight into the etiology of this tumor. Mutations of the GSK3β binding domain of *CTNNB1* have been identified in other lesions, including calcifying odontogenic cysts and pilomatricoma [7, 16, 19], a benign skin tumor that is histologically characterised by anucleate squamous cells, similar to ACP. As such, ACP shares genetic and histological characteristics with tumors of odontogenic origin. However, it has been postulated that ACP arises from undifferentiated anterior pituitary epithelial stem cells and differentiates toward an oral epithelial phenotype [18, 20, 23, 24]. One model proposes that there is a small population of mutated cells, which express nucleocytoplasmic β-catenin, which are histologically identified within well-demarcated clusters [17]. This theory is supported by recent in vitro and animal models that are discussed in Chap. 2 and 3. Briefly, a leading hypothesis regarding ACP tumorigenesis is that para−/autocrine signaling emanating from this small population of *CTNNB1* mutated cells (i.e. cancer stem cells) and that this drives tumor growth and invasion. It has also been postulated that microRNA derangements also in part help drive tumor behaviour [7]. It may therefore be that, while the tissue of origin differs, the phenotypic maturation of ACP tissue converges with that of odontogenic lesions [25, 26].

Epidermal Growth Factor Receptor

Although genome level dysregulation of the epidermal growth factor pathway does not appear to exist in ACP, there is evidence that upregulation of this pathway, potentially by epigenetic mechanisms, contributes to ACP cell growth and infiltration.

The epidermal growth factor receptor (EGFR) is a 170 kDa receptor tyrosine kinase (RTK) that is also known as HER1, ErbB1, mENA, and PIG61 [10, 18]. It is a transmembrane glycoprotein composed of an extracellular domain that is involved in ligand binding, a transmembrane portion, and an intracellular portion that makes up the tyrosine kinase domain and is the site for autophosphorylation [18]. EGFR can be activated by multiple growth factors, including epidermal growth factor (EGF), TGF-α, amphiregulin, epiregulin, heparin-binding EGF (HB-EGF), and betacellulin [18]. When the ligands bind the extracellular domain, the receptor undergoes dimerisation, which activates the intracellular tyrosine kinase domain. This results in phosphorylation of multiple tyrosine residues (e.g. Y992, Y1045, Y1068, Y1086, Y1148, and Y1173) [11, 18]. Binding of the ligand to the extracellular domain also promotes recruitment of other enzymes and proteins, which act as signal transducers and can lead to initiation of multiple intracellular cascades involved in regulation of cell proliferation, differentiation, apoptosis, and motility [18]. Alterations in EGFR signaling have been noted in multiple human tumor types [20] resulting from various mechanisms including EGFR gene amplification, activating mutations, or overexpression of ligands and receptors [18]. In some tumor types, a common location for mutation is the area that encodes the tyrosine kinase domain of EGFR, between exons 18 and 21 [18].

The mechanism of EGFR pathway contribution to ACP behaviour may lie in the interaction between EGFR and β-catenin [12, 18, 27]. When activated and phosphorylated, one interesting proposed mechanism is that EGFR co-localises with nuclear β-catenin and fascin, particularly at the infiltration border of ACP, within whorl-like cell clusters [12, 18]. As described above, in ACP, these clusters have been associated with activation of the canonical Wnt signaling pathway. This suggests a convergent role for both the EFGR and Wnt pathways in the pathogenesis of ACP [18]. This concept is supported by laboratory data [10, 20] and culture models that correlate EGFR pathway activation with ACP growth and migration of ACP cells [18]. Additionally, EGFR appears to be involved in the regulation of stem cell like properties in ACP through the regulation of the expression of stem cell markers and the activation of the EGFR pathway in β-catenin accumulating cells [5]. Lastly, the ACP transcriptome demonstrates high levels of EGF pathway genes, including *AREG*, *EGFR*, and *ERBB3* [20].

SHH

Sonic hedgehog (SHH) plays an integral role in the maintenance of stem cell milieus in adult tissues [28] and in the normal development of several organs, including Rathke's pouch [12]. The SHH pathway is involved in pituitary formation during early embryogenesis. The transmembrane protein Patched 1 (PTCH1) receptor complex binds the hedgehog ligand, which activates the pathway [22]. Once the ligand binds to the receptor complex, the frizzled class receptor, smoothened (SMO), is freed from PTCH1 inhibition. It then activates glioma-associated oncogene family zinc fingers—the GLI1, GLI2, and GLI3 transcription factors [22]. Pathological upregulation of SHH signaling contributes to mitogenic behaviour in numerous neoplasms, including glioma, basal cell carcinoma, lung cancer, and breast cancer [28, 29]. Among pediatric brain tumors, the most widely known example of hedgehog dysregulation is in the SHH subgroup of medulloblastoma [1].

As described in Chap. 2, expression of SHH has been observed in a murine model of ACP and in human ACP. In both mouse and human tissues, expression of SHH has been shown to co-localise in cells that have distinct nuclear localisation of β-catenin [28]. The pattern of expression, combined with our understanding of the SHH pathway in normal human pituitary development, supports the hypothesis that both autocrine and paracrine SHH signaling may contribute to ACP tumorigenesis. The importance of SHH signaling in the pathogenesis of ACP has been supported by two studies of the human ACP transcriptome, both of which have demonstrated significant upregulation of SHH pathway genes [20, 22] [Fig. 2]. In addition, a very recent study comparing the transcriptomes of ACP with PCP showed significantly higher expression of SHH pathway genes *Axin2*, *Gli2*, and *PTCH1* in ACP [25]. This important finding further supports the possibility of WNT and SHH signaling pathways converging to support the growth of ACP. This study also showed that methylation profiling patterns are distinct between ACP and PCP, further establishing that ACP

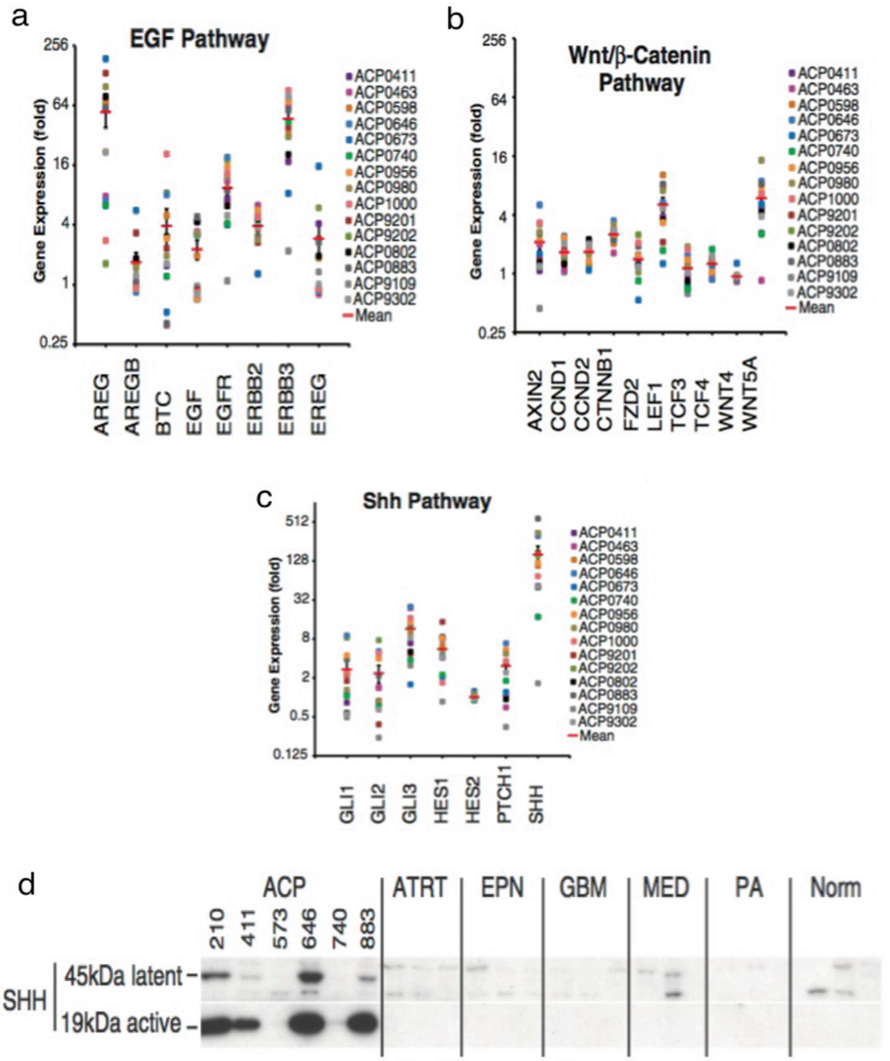

Fig. 2 Expression of the indicated developmental and cancer-related genes in individual ACP samples: (**a**) Epidermal growth factor genes; (**b**) WNT pathway; (**c**) Sonic hedgehog pathway; (**d**) Western blot analysis demonstrating overexpression of the latent pre-forms and active cleaved protein isoforms of SHH in ACP relative to other common pediatric brain tumors and normal brain. *AT/RT* atypical teratoid/rhabdoid tumor, *EPN* ependymoma, *GBM* glioblastoma, *MED* medulloblastoma, *PA* pilocytic astrocytoma, *Norm*, normal brain). Adapted from Gump et al. [20]

and PCP are indeed biologically distinct lesions with different mechanisms of pathogenesis.

Additional Potential Relevant Pathways

In addition to the activation of EGFR and SHH pathways that we describe above, other molecules and pathways have been demonstrated to be uniquely expressed in craniopharyngioma, but are not yet as well described. As effective therapy for any brain tumor, including ACP, is likely to require multiple medications, further exploration of these pathways has clinical relevance.

Two studies of the ACP transcriptome found upregulation of certain matrix metallopeptidases [20, 30]. Gong and colleagues identified elevation of MMPs 2, 3, 7, and 9 in recurrent ACP, relative to primary ACP. Gump and colleagues [20] identified elevated levels of MMPs 9 and 12 mRNA transcripts in pediatric ACP, relative to other brain tumors and normal brain. The clinical relevance of these findings is increased by the availability of the oral MMP9/12 inhibitor, AZD1236. The latter group additionally identified the upregulation of three targets of the oral tyrosine kinase inhibitor dasatinib (EPHA2, LCK, and SRC), thereby revealing another potential therapeutic option [20].

Elevated levels of p63 have been identified in both ACP and PCP. P63, also known as p51, p40, p73L, or KET, is a gene homologue of the p53 tumor suppressor family. The gene has two separate promoters, which result in different isoforms, one with an N-terminal transactivation, and one that lacks this N-terminal domain. These two isoforms have opposite functions and are responsible for cell-cycle arrest and proliferation [19]. Using immunohistochemistry, p63 nuclear immunopositivity was identified in both ACP and PCP [10, 19]. Evidence of p63 expression was also identified in the ACP transcriptome [20]. While p63 is suggested to play a key role in the control of epidermal proliferation and differentiation, impaired p63 expression has also been recently seen in squamous cell carcinomas arising in different organs and has been suggested to influence neoplastic cell transformation [19].

Papillary Craniopharyngioma

Distinction from ACP

As described above, the distinct mutations identified in ACP and PCP, the different transcriptome profiles, and the differences in genome wide methylation patterns support the view that ACP and PCP are biologically distinct entities with different mechanisms of pathogenesis. These genomic studies support the earlier findings

from histological studies that demonstrated nuclear and cytoplasmic accumulation of β-catenin in ACP whereas β-catenin localised exclusively to the cell membranes of tumor cells in PCP, similar to the pattern of localisation in other *CTNNB1* wild type tumors of the sellar region [10, 12, 16, 19].

BRAF

Mutation of the *BRAF* gene results in oncogenic potential through constitutive activation of a serine-threonine kinase that regulates MAP kinase signaling and affects cell division and differentiation. A multitude of human tumors harbor *BRAF* anomalies, most commonly *BRAF* V600E mutation. Successful therapy has been reported in cutaneous melanoma [31, 32] in addition to less common lesions, including ameloblastoma [33], hairy cell leukemia [34], and pleomorphic xanthoastrocytoma [35]. As described above, a recent genomic analysis of PCP [21] used a combination of whole exome sequencing and targeted genotyping. In this study, *BRAF* V600E mutations were identified in 92.8% of PCP specimens, but none of the ACP specimens examined. Notably, only three PCP specimens were analysed with whole exome sequencing of both normal DNA and PCP tumor DNA, thus the presence of other lower frequency recurrent genomic events in PCP cannot be entirely excluded. Additional studies have validated that nearly all PCP harbor *BRAF* V600E mutations [36–38]. One report suggests that a subset of craniopharyngioma may harbor coexisting mutations in both *CTNNB1* and *BRAF* genes [8]. Such a co-occurrence of mutations would be of great clinical interest and warrants further exploration and validation.

The potential clinical significance of *BRAF* V600E mutation in PCP has been described with regard to both diagnosis and therapy. A mutation-specific antibody (clone VE1) which recognises the BRAF V600E mutant protein but not the wild type protein [39] is now routinely used in clinical practice to support the diagnosis PCP and to help distinguish it from other masses of the sellar lesion including pituitary adenomas, ACP, and Rathke's cleft cysts [36, 38, 40]. Despite cross-reactivity with normal pituicytes and with ciliated cells, this antibody generally allows pathologists to rapidly and inexpensively confirm the diagnosis of PCP. Difficult cases can be assessed using targeted genotyping of the BRAF V600E mutant allele.

From a therapeutic standpoint, the combination of the RAF inhibitor dabrafenib and MEK inhibitor trametinib was recently used to successfully treat an adult patient with a multiply recurrent craniopharyngioma [41]. This patient had an exceptional response to treatment [Fig. 3]. Despite the frequent development of resistance to BRAF and MEK inhibitors that emerges in melanoma patients, whole exome sequencing failed to find evidence of such genetic resistance mechanisms in the PCP tissue that remained post-treatment. The rationale for targeting both BRAF and MEK is supported by the recent example of a patient with a BRAF V600E mutant PCP that was treated with single agent vemurafenib [42]. That tumor was

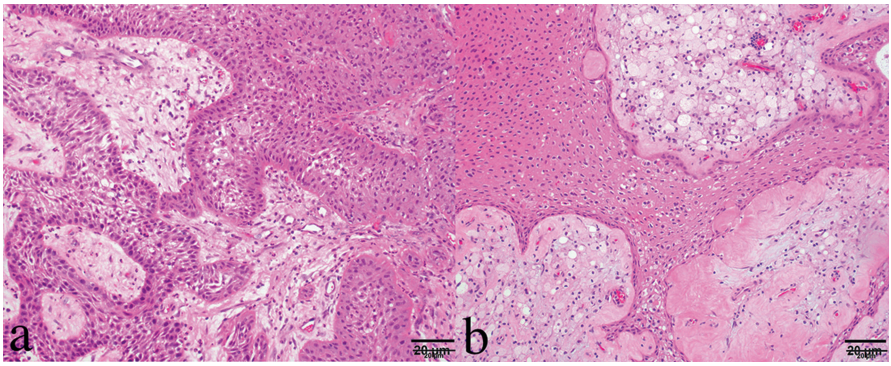

Fig. 3 Effect of dual therapy using dabrafenib and trametinib on multiply recurrent papillary craniopharyngioma. Haematoxylin and eosin stained specimens prior to (**a**) and following (**b**) treatment. Note the absence of epithelial tumor components and the engorgement of some fibrovascular cores with foamy macrophages

also exceptionally responsive to targeted treatment, however, when vemurafenib treatment was stopped the tumor regrew and subsequently became refractory to vemurafenib. This example suggests that combining BRAF and MEK inhibition may be needed for durable control of tumor growth.

A multi-institutional phase II study of combined BRAF and MEK inhibition for patients with PCP is forthcoming [43]. This trial will allow for correlative studies to assess if mechanisms of resistance emerge post-treatment as well as whether mutant DNA can be reliably detected in the patients' blood as a non-invasive means for diagnosis and monitoring therapy.

Summary

Over the last decade, substantial progress has been achieved in our understanding of the processes underlying craniopharyngioma pathogenesis. Genomic studies have identified distinct epigenomic and mutational profiles in the vast majority of ACP and PCP tumors. Thus, ACP and PCP are distinct entities and will require distinct therapeutic approaches. In the case of PCP, advances made in the context of other tumors that harbor *BRAF* mutations have facilitated the initiation of clinical trials of novel systemic therapies for this tumor. In the case of ACP, therapy directed at inhibiting β-catenin is not yet available. However, evidence from both genome and transcriptome studies has implicated additional opportunities such as the SHH and EGFR signaling pathways and matrix metalloproteinases that offer more readily available therapeutic options. Further validation of these findings may soon advance biomarker driven and molecularly guided systemic therapies for ACP as well.

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