# Current Opinion on Craniopharyngioma Biology

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**Over the recent years, a considerable number of studies devoted to craniopharyngioma morphology have been performed. Over 35 factors that could be related to the craniopharyngioma growth are known: Ki-67, p53, beta-catenin, p63, Retinoic acid receptors, Galectin-3, MIF, MVD, CK, etc. Despite such a variety of factors, none of them, except for Ki-67, strongly correlates with the risk of tumor recurrence and none can be associated with a particular tumor type. Most studies have focused on a very small number of factors and have been carried out in relatively small groups of patients. Most publications have been devoted to the Ki-67, beta-catenin and p53, and the largest number of patients enrolled in the study was 67. In this survey, we made an attempt to review the literature on craniopharyngioma biology and to identify further research areas to obtain data that could affect the choice of treatment and outcome of this complex disease.**

*Keywords: craniopharyngioma, biology, growth factors, Ki-67.*

**Abbreviations:**

CP – craniopharyngioma

ACP – adamantinomatous craniopharyngioma

PCP – papillary craniopharyngioma

MVD – microvascular density

VEGF – vascular endothelial growth factor

MIF – macrophage-inhibiting factor

WNT (a combination of the Drosophila gene known as **Wg** (wingless) and the homologous vertebrate gene **Int**) – the name of a complex cascade of a large number of proteins that form the so-called signaling pathway participating in embryogenesis, tissue differentiation, and cancerogenesis

Ki-67 – cell proliferation marker

MIB-1 – clone of anti-Ki-67 antibody.

Craniopharyngiomas (CP) are benign epithelial tumors arising from the remnants of epithelial tissue in the improperly formed pituitary gland or the remnants of the craniopharyngeal duct [30]. CP can be formed in any segment of the craniopharyngeal duct: from the sella turcica to the hypothalamus, and can also occur in the adjacent regions from the nasopharynx to the ventricular system [5, 10, 20, 22, 23, 42].

Despite the histologically benign properties, macroscopically radical resection of CP is associated with a high risk of relapse, reaching from 30% (during the 10-year postoperative period [12]) to 59% (during the 5-year postoperative period [60]). Surgical resection is still considered to be the main method for managing CP. According to different data [7, 36, 52, 61, 62, 69], the probability of radical resection is 50–80%. The current data regarding the efficiency of postoperative radiation are rather ambiguous: from attaining 95% recurrence-free survival [59] to the total inefficiency [60].

CP account for 2–5 and 5.6–13% of all intracranial tumors in adults and children, respectively [46, 53]. The peak incidence of CP is observed in two age groups: 5–14-year-old and 50–74-year-old patients [6].

## CP Structure and Mechanisms of Formation

### 1. Hypotheses of CP formation

The mechanisms of CP formation remain unelucidated. The only fact is known for sure: these tumors are congenital and are most likely to be nonheritable. The reasons for growth initiation in different age groups are unclear. A number of possible and interrelated processes are currently being discussed:



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– cell proliferation caused by disorders of apoptosis (programmed cell death) – activation of anti-apoptotic mechanisms and/or disturbance in sensitivity to growth factors;

– development of cell anaplasia;

– tumor cells acquire properties causing local invasive growth;

– neoangiogenesis – formation of blood vessel neoplasms in tumors, resulting in tumor growth.

There are two main acknowledged theories of CP formation: the theory of embryogenesis and the metaplastic one. The former theory proposes that the remnants of pharyngeal epithelium and/or the Rathke's pouch undergo tumor transformation during the development of the anterior pituitary gland. This mechanism presumably bolsters the formation of adamantinomatous craniopharyngiomas (ACP) that most frequently occur among children. The latter theory suggests that metaplasia of the remnants of stratified squamous epithelium develops, giving rise to papillary craniopharyngiomas (PCP) in adults [6, 34, 39, 66].

## 2. Morphological characteristics of CP

Only 10% of CP have a completely solid structure. The remaining 90% of tumors are characterized by the formation of cysts with different volume. In 60% of CP, the cystic component predominates with respect to its volume [2].

The histological structure of CP is represented by two variants: adamantinomatous and papillary CP, which differ considerably in terms of their biological and clinical behavior.

ACP predominantly occur among children, young people and, less frequently, in elderly people. The histological presentation includes growth of epithelial cells that form bundles of trabecules and round aggregates. The appearance of epithelium differs depending on its localization: the basal layer adjacent to the connective tissue is formed by a single layer of oval cells; the further epithelial cells are less ordered. As they approach the center of the aggregate, the epithelial cells acquire syncytial structure (stellate shape of the cells) and form reticular structures resembling the enamel organ. This CP variant is frequently associated with the development of ceratoid degeneration, formation of horny lamellae and giant-cell granulomas of foreign bodies. The calcification and ossification phenomena are quite typical [24].

Unlike ACP, PCP occur in adults, have a more compact solid structure, and are less likely to contain cysts and petrificates. PCP are formed by well-differentiated epithelium. The layers of stratified non-keratinized squamous epithelium are separated by a loose connective tissue stroma containing a large number of vessels. The mutual arrangement of the stroma and epithelial layers forms papillary structures that are morphologically similar to squamous cell papilloma [14, 31]. PCP containing goblet and ciliated cells are also known as ciliated CP. According to K. Sato [54], they are formed from the basal cells of Rathke's pouch cysts via squamous metaplasia. According to the WHO classification, CP are grade 1 benign tumors.

### *2.1. Local invasive growth of CP*

Despite their benign nature, CP are prone to infiltrative growth. This occurs due to focal invasion of individual epithelial aggregates to the adjacent brain tissue. These aggregates of tumor cells result in reactive changes in the glial tissue accompanied by the formation of the so-called glial pseudocapsule of CP, which can sometimes be misinterpreted as pilocytic astrocytoma.

The electron microscopic studies of the wall fragments of the third ventricle that had been resected along with CP demonstrated that the apical regions of ependimocytes form folds and lose the "cilia"; however, they acquire a number of multioriented microvilli. The surface cells flattened and sparse; they have a polygonal shape with 3–7 protruding facets. An ultrastructural analysis reveals the existence of various types of several layers of ependymal and subependymal epithelium. Both types of epithelium contain numerous neurofilaments and well-pronounced intercellular contacts. In addition, the foci of cellular disorganization have also been detected [48, 49].

### *2.2. Epidermal growth factor receptor (EGFR)*

EGFR plays an important role in tumor cell migration and infiltration of the medullary substance of ACP. Neither mutations nor amplifications of the *EGFR* gene have been detected by genetic study of ACP. Nevertheless, activated (phosphorylated) EGFR was detected in tumor fragments infiltrating the medullary substance and localized together with beta-catenin and fascin. Activated EGFR induces tumor cell migration [17].

### *2.3. Malignization of CP*

Malignization of CP occurs rather rarely, in most cases after multiple relapses and radiation. Less than 10 cases of malignant transformation of CP have been reported.

In 2010, M. Ishida [19] reported malignant transformation of CP in a patient who underwent two surgeries and a course of radiation therapy. The bioptates obtained during the first and second surgery were characterized by the typical morphological presentation of ACP. Large foci of basaloid cells with large oval nuclei containing a clearly define nucleolus and frequent mitotic figures the tumor (21/10 of the field) were obtained during the third surgery. The p53 expression was higher as opposed to that in the "benign" regions of the tumor. The fact of tumor malignization was ascertained according to this presentation.

In other studies where malignization of CP was reported, all patients underwent radiation therapy, and high p53 expression in tumor cells was observed in all the cases.

A single case of primary malignant CP has been reported in literature; earlier treatment and radiation were not specified. The nests of epithelial basaloid cells with round to oval nuclei, intense polymorphism, nuclear hyperchromasia, an increased nuclear:cytoplasmic ratio, and high mitotic activity were detected microscopically in the tumor tissue. The immunohistochemical data revealed high Ki-67 labeling indices (44.3%), p53 (98%), and p63 (100%) [4].

Furthermore, a single case of malignant transformation of CP to squamous-cell carcinoma has been reported [26].

## 3. Proliferation and neoangiogenesis as factors of CP progression

### *3.1. Ki-67 antigens (antibodies, clone MIB-1)*

Ki-67 protein is a marker of cell proliferation. MIB-1 monoclonal antibodies are used to detect Ki-67 antigen [55]. The labeling index for proliferation markers is low in most CP [65].

The Ki-67 labeling indices (MIB-1 clone) in epithelial cells were found to be higher than those in the tumor stroma; the expression is predominantly detected in palisade cells of the epithelial component along the peripheral regions of the epithelial complex.

The MIB-1 labeling index is not an independent criterion of the relapse risk. It lies within the range of 0.1–34.6% (mean value 8.9%; SD 9.8) in adults. In children, it remains within the range of 1.8–15.0% (mean 6.3%; SD 3.7). The MIB-1 labeling index is not considered to be an independent criterion of the relapse risk; however, an increase in this index was observed in children with recurrent CP for each subsequent episode of tumor emergence. The Ki-67 labeling index is used to assess the tumor nature and aggressiveness [44]. According to the other data, the MIB-1 level can vary from 0.4 to 32.5% (mean 10.84%). The MIB-1 level turned out to be 3.4±2.3% in patients with non-recurrent CP. The MIB-1 labeling index for the recurrent tumors was considerably higher (13.2±7.7%).

The "threshold" level of the MIB-1 labeling index (7%) was statistically determined in some studies; above this level, the risk of tumor recurrence significantly increases [37].

The MIB-1 level in adult CP is higher than that among children. The epithelial cells of CP adjacent to the stromal cysts are more active as compared to those being adjacent to the neural tissue. The accumulation of MIB-1 in nuclei differs for the two types of CP [12].

According to some data, the MIB (Ki-67) level is identical for ACP and PCP [12]. However, other data reported that the Ki-67 labeling index and the microvascular density index were stronger pronounced in ACP as compared to those in PCP (22±6 vs. 17±3, $p$=0.05; 21±3 vs. 17±3, $p$=0.037); these indices were associated neither to the recurrence nor to the continued growth [60].

The Ki-67 (MIB-1) index is considerably higher in the malignized regions. Malignization of CP is a very rare phenomenon; it occurs after multiple relapses and radiation [51].

### *3.2. The p53 protein and p53-related proteins p73 and p63*

The p53 protein participates in DNA repair processes and in regulation of transcription of the genes regulating apoptosis. An increase in the p53 level in response to DNA damage typically induces apoptosis [32].

When studying the p53 level, expression of its mutant form (i.e., the form that cannot regulate apoptosis) is detected in both ACP and PTP [35].

The presence of concentric foci of epithelial cells in the tumor ($p$=0.04) and high level of p53 expression ($p$=0.022) reliably correlate with the risk of continued growth and probability of relapse [60].

The p63 and p73 proteins are considered to be oncosuppressors. High level of p63 expression is detected in all cellular layers; while p73 expression (from moderate to high) is detected only in the basal cellular layers [35].

The p63 protein participates in regulation of adhesion and viability of epithelial cells [9].

The increased level of p63 expression is detected in most ACP and PCP, which is accompanied by an increased level of the deltaNp63 mRNA isoform [8]. The deltaNp63 isoform is expressed in squamous-cell carcinoma and presumably plays a role in enhancement of aggressiveness in biological behavior of CP cells [35].

In the study conducted by Zh.B. Semenova (Burdenko Neurosurgical Institute) in 2000, no expression of p53, carcinoembryonic antigen, and epithelial membrane antigen has been detected in any of 62 observations. Tenascin expression was detected in the basal membranes and fibroblast cytoplasm. High expression of cer B-b2 oncoprotein was revealed only in ACP (30–100% of cells were stained). Direct correlation between the expression of cerB-b2 and Ki-67 has been established. Furthermore, the Ki-S1 labeling indices were studied (the level varied from 0.3 to 12%). The highest indices were detected for the recurrent tumors. The average level of the labeling index for the proliferating cell nuclear antigen (which was mostly detected in ACP) was 25% and varied from 12 to 45%. The distribution of stained nuclei in all the cellular layers was absolutely homogeneous [1].

### *3.3. Microvascular density (MVD)*

Vascular malformation in the tumor due to proliferation and migration of endothelial cells are one of the key possible mechanisms that explain the aggressive behavior of CP.

The MVD of the tumor can be assessed immunohistochemically using anti-endothelial marker CD34 monoclonal antibodies. The CD105 antigen is reported to be a more specific endothelial marker than CD34 [11].

The MVD level assessed using CD105 turns out to be considerably lower than that determined using CD34 [11]. It is noteworthy that only 2.5% of vessels stained with CD34 in ACP express the vitronectin (VTN) receptor – integrin alpha-V beta-3 ($\alpha_v\beta_3$) [65]. Vitronectin participates in regulation (suppression) of proteolysis, which is initiated by plasminogen activator (whose high level determines activity of angiogenesis processes and the tumor growth rate). The low level of integrin alpha-V beta-3 correlates with active angiogenesis and high tumor growth rate [16, 38, 68]. A positive correlation between the MVD value and the Ki-67 labeling index (clone MIB-1) was detected [65].

Pathohistochemical studies reveal a relatively small number of capillaries in the tumor stroma, as opposed to its epithelial component. The immunohistochemical test reveals the expression of vascular endothelial growth factor (VEGF) in epithelial cells of both CP variants (adamantinomatous and papillary CP). The *in situ* hybridization (ISH) method detects expression of mRNA of VEGF receptor-2 (VEGFR-2) both in the endothelial component of the tumor and in capillary endothelium.

VEGFR-2 is the key modulator of VEGF activity in endothelial and stromal cells as it plays a significant role in aggressive behavior of CP [64].

Some alternative opinions have also been put forward. According to them, the levels of VEGF and endostatin expression in the epithelial component, as well as the expression levels of other stimulators and inhibitors of angiogenesis are independent of the intensity of MVD [11].

#### 4. Craniopharyngeal cysts and interferon

An assumption has been made that cyst formation in the CP tissue is associated with the level of VEGF expression. VEGF expression in CP with predominantly cystic structure is considerably higher than that in tumors with predominantly solid structure or the ones containing few small cysts, where there may be no VEGF expression at all [63].

A lot of aspects of the mechanism of formation of cystic fluid in CP still remain unclear. Two theories are predominantly discussed: (1) cystic fluid is formed as a result of permeability of the hematoencephalic barrier; (2) it is secreted by the capsule.

Alpha-defensin 1–3 proteins is a crucial component of the cystic contents; its presence may indicate that the immune system participates in cyst formation.

Human alpha-defensin 1–3 accounts for 30–50% of all the proteins in azurophilic granules of neutrophil segmentonuclear leukocytes, which are cells with the known and high antibacterial and antiviral activity. The level of alpha-defensin expression is significantly increased in saliva of patients with squamous-cell carcinoma of the oral cavity, in contents of jaw cysts, and in the plasma of patients with sepsis and meningiomas. Furthermore, the expression level of these proteins decreases after alpha-interferon is injected to the cyst, which correlates with the further clinical outcome.

The possible mechanism of action of interferon participating in this effect has not been elucidated yet: it may exert either a direct effect on squamous epithelial cells of the cysts or an immunomodulating effect due to initiation of the immune system [40, 45].

Antimicrobial protein alpha-defensin 1–3, which is responsible for initiation of the immune response had been detected in cystic fluid of CP before the therapy was started. The protein level considerably decreases in patients who receive conservative treatment. The clinical treatment outcomes correlate with gradual reduction in the level of alpha-defensin 1–3. Detection of alpha-defensin 1–3 eliminates the disturbance of the hematoencephalic barrier from being regarded as a possible reason of formation of cystic fluid and verifies the fact that the immune response participates in cyst formation. The antitumor effect of interferon still needs to be refined [41].

**Carboanhydrase IX (CA IX)** is an enzyme associated with the tumor and induced by hypoxia; this enzyme cannot be associated with the formation of cystic fluid. In healthy patients, CA IX is not detected in brain tissues; its expression is inhibited by p53 protein.

M. Proescholdt et al. [43] have studied 20 CP samples and found a significant level of CA IX in 85% of cystic CP; the expression intensity correlated with the cyst size. No p53 mutations were detected in the CP studied.

The authors additionally studied expression of **HIF-1alpha** (the hypoxia-inducible factor, which is a transcription factor that responds to the changes in oxygen level in the cellular environment resulting in hypoxia) and found no correlation with the cyst size. According to their data, HIF-1alpha most frequently is not detected in tissues where a high level of VEGF expression was observed.

Authors [43] have ascertained that the regulation mechanism of CA IX has not been thoroughly elucidated; however, neither hypoxia nor p53 plays a significant role in it. They believe that the inhibition of CA IX may turn out to be a potential "target" for the adjuvant targeted therapy of cystic PC.

#### 5. Molecular and genetic features of PC

Mutant D32Y, G34R, and G34V genes, which occur in some skin neoplasms were detected in epithelial cells of CP [25].

CP are monoclonal tumors that are formed after activation of oncogenes localized in certain chromosomal loci. Most tumors are characterized by increased *DNA copy number*. Reduced copy number is detected much less frequently [47]. Polysomia or chromosomal loss are not typical of primary tumors in the pediatric population. M. Yoshimoto et al. [67] believe that this fact indicates that chromosomal dysbalance does not play a crucial role in the formation of these tumors in children.

Studies of the nuclei of epithelial cells of ACP, which accumulate beta-catenin, have shown an increased expression level of the Axin-2 and BMP4 (bone morphogenetic protein 4) genes. The increased BMP4 expression level supports the theory that ACP is formed from the oral ectoderm. Furthermore, exon 3 mutations were detected in cells accumulating (ACP) and not accumulating (PCP) beta-catenin. No disruptions in the genes responsible for the membrane bonds and active/passive nuclear transport (exons 4, 8–13) have been revealed [18].

### *5.1. Beta-catenin and WNT signaling pathway*

The WNT signaling pathway [50] is a complex cascade of a large number of proteins participating in embryogenesis, tissue differentiation, and cancerogenesis [29]. The disturbance of the WNT signaling pathway is one of the molecular mechanisms of neoplastic cell transformation that is typical of ACP and presumably causes the infiltration of the adjacent brain tissue [18].

Membrane receptors associated with WNT normally initiate the intracellular signaling cascade, resulting in inactivation of the cytoplasmic synthase kinase-3beta (GSK3beta) complex. This proteosomic complex participates in degradation of beta-catenin. The inactivation of the complex causes transfer of beta-catenin molecules to cell nuclei, where they interact with the TCF family of transcriptional factors (T-cell factor/lymphoid enhancer factor). The resulting intracellular accumulation of beta-catenin enhances the expression of target genes, such as c-myc and Cyclin D1 and plays the key role in proliferation and formation of cell structure and polarity. In other words, accumulation of beta-catenin in cellular cytoplasm or nuclei stimulates proliferation of tumor cells and inhibits apoptosis. GSK3beta mutations have recently been detected in ACP. Furthermore, this mutation causes the disturbance of the Axin2 gene expression in CP. An increased Axin expression level is the manifestation of the negative association with beta-catenin activity. Increased Axin activity causes degradation of beta-catenin and reduction in its cellular concentration [40]. The WNT–beta-catenin–TCF complex is believed to play a crucial role in the formation of PC [15].

Beta-catenin is accumulated in ACP in nuclei or the cytoplasm of the cohesive cells localized in the concentric foci and in cells that can be transformed to the ghost cells (that never express Ki-67). The cohesive cells in the concentric foci do not express cytokeratins. Hyperexpression of beta-catenin in cellular nuclei of typical ACP correlates with heterozygous mutations of the beta-catenin gene. Nuclear expression of beta-catenin is not observed in ACP with irregular structure and PCP with the well-defined squamous component. These tumors show no mutations in the beta-catenin gene. These data attest to the morphogenetic heterogeneity of CP. The pathogenesis of typical ACP is associated with the disturbance of the WNT-signaling system, transducing a greater signal to the morphogenesis of concentric foci and ghost cells as compared to the other proliferative stimuli [24].

Furthermore, beta-catenin expression in some cases was detected in palisade cells, where Ki-67 was typically detected [8].

ACP and PCP differ clinically, morphologically, and genetically as well. The mutant beta-catenin gene was detected only in ACP. In all the cases, beta-catenin was accumulated both in the cytoplasm and cellular nuclei of these tumors. PCP are characterized by the membrane expression of beta-catenin only. In addition, the mutant beta-catenin gene was detected both in the epithelial and mesenchymal cells of ACP, which attests the biphasic nature of these tumors [57].

### *5.2. Odontogenic proteins*

ACP are characterized by histological similarity with some odontogenic tumors (ameloblastoma, calcifying odontogenic cyst), although no data have been obtained supporting the fact that ACP develops from odontogenic epithelium [58].

The LEF1 protein factor, which gives rise to tooth enamel, is expressed only in tooth and plays a significant role in tooth development along with beta-catenin. The emergence of this factor and other odontogenic proteins is indicative of odonotogenic differentiation of epithelium.

ACP are characterized by odontogenic epithelial differentiation. Different levels of expression of enamel proteins (including amelogenin, enamelin and enamelysin) were revealed in all ACP, predominantly in the ghost cells. LEF1 was also heterogeneously expressed in ACP, in a manner similar to the accumulation of beta-catenin in cell nuclei. Expression of enamel proteins and LEF1 has been detected in none of PCP.

A hypothesis has been made that it is accumulation of beta-catenin that activates transcription of the beta-catenin/LEF1 complex, which may play a crucial role in tumor formation [58].

### *5.3. Oncogenesis markers*

#### *5.3.1. Cytokeratins*

Cytokeratins (CK) are the proteins forming intracellular intermediate filaments of the epithelial cell cytoskeleton of [56]. Controversial data were obtained by assessing the expression levels of CK in CP. Some researchers have found that CK8 is detected in most CP, while CK20 is predominantly revealed in the Rathke's pouch cysts [27].

The other authors [66] report that, unlike the cysts in the Rathke's pouch and the intermediate lobe of hypophysis, CP do not express CK8 and CK20. When studying the recurrent CP, CK8/CK18/CK19 expression was detected in 64% of tumors; expression of CK5, laminin 8, and carcinoembryonic antigen was detected

in 42, 62, and 21% of tumors, respectively. No significant difference between the expression levels of CK, laminin, carcinoembryonic antigen, and gliofibrillar acid protein (GFAP) was detected in ACP and PCP [60].

*5.3.2. Cathepsins*

Intracellular proteases (cathepsins) are believed to actively participate in oncogenesis. More than 15 cathepsin are known today.

Cathepsin B is a cysteine protease [3]. Cathepsin B expression increases when the primary brain tumors are malignized; however, its level shows no correlation with the aggressiveness of CP [33]. Being an aspartic protease, cathepsin D is associated with tumor invasiveness [13]. According to other reports [33], it is detected in prostate cancer cells, where it participates in production of angiostatin, the potential angiogenesis inhibitor that decelerates the growth of the primary tumor and angiogenesis-dependent metastases. The increase in cathepsin D level in CP cells (that are typically better differentiated) increases the angiostatin level, reduces the risk of relapse, and slows down the growth rate of CP.

Cathepsin K is a cysteine protease belonging to the papain class. It is capable of degrading osteoproteins: type I collagen, osteopontin and osteonectin, thus causing osteoporosis. The increased cathepsin K level was detected in recurrent CP characterized by reduced cell differentiation [33].

The expression intensity of cathepsins D and B show a good correlation with the expression level of retinoic acid receptor (RAR)-beta, while the expression level of cathepsin K correlates with that of RAR-gamma. The recurrent CP are characterized by an increased cathepsin D level and reduced cathepsin K level [33].

*5.3.3. Macrophage migration inhibitory factor*

The macrophage migration inhibitory factor (MIF) is presumably another factor of CP oncogenesis. MIF mRNA (matrix ribonucleic acid) is normally expressed in skin and nerve cells; the effect of MIF has been described for various skin pathologies and varied from inflammation to hyperplasia. MIF is believed to stimulate tumor growth and angiogenesis, since anti-MIF antibodies efficiently terminate the aforementioned processes. MIF expression correlates with the risk of recurrent CP [40]. According to other data [28], the MIF level in cells of CP with rapid recurrence was found to be considerably lower than that in cells of tumors with slow recurrence.

*5.3.4. Galectin*

A decreased galectin-3 level is also observed in CP with rapid recurrence. The antiapoptotic role of galectin-3 is determined by its participation in phagocytosis, while the reduction in its level disturbs the usual biological elimination of the remnant embryonic tissues [28, 40].

**6. Sex hormone receptors in CP cells**

***6.1. Estrogen and progesteron receptors***

An increased level of mRNA expression for estrogen and progesterone receptors is revealed in proliferating epithelial CP cells. These receptors can be markers of the potentially high tissue differentiation, since their co-expression is associated with a low risk of tumor recurrence [21].

***6.2. Retinoic acid receptors and cathepsins***

Retinoic acid receptors (RAR) are a group of nuclear to steroid and thyroid hormone receptors. Several isoforms of these receptors are known: alpha, beta, and gamma. There is clear dependence between anaplasia with the risk of CP recurrence and RAR expression. RAR are one of the biological regulators of maturation of various endothelial types, including epidermal tissue. Correspondingly, the level of various RAR isotypes differs depending on the level of maturation and differentiation of epidermal cells. A reduced level of RAR-beta and increased level of RAR-gamma isotypes have been detected in recurrent ACP [33].

## Conclusions

It should be mentioned that a significant advances in studying CP morphology have been achieved over the past decade. The number of various factors associated with the development of CP, which can be assessed using different methods, approaches 40 **(see Table)**.

The available data illustrate that ACP and PCP are morphologically different tumors, which requires one to use the differentiated approach in further research.

After we have compared different studies used to prepare this review, we can claim that none of these studies was comprehensive. The largest number of observations was no greater than 60. ACP was the most frequently studied type of CP. The number of markers analyzed in a single study was no greater than 6–8.

It is obvious that the next stage, in addition to revealing new oncogenetic factors, should consist in analyzing the relationships between the data that have already been obtained in various studies and the clinical outcomes of different treatment options of CP. The aim of this analysis is to determine the most significant prognostic criteria of the risk of rapid progression and emergence of recurrent craniopharyngiomas. The Burdenko Neurosurgical Institute is a specialized neurosurgical hospital where some 100 patients with craniopharyngiomas, both adults and children, are annually operated. Such a topical clinical and morphological study can be carried out using the facilities of this institution.

Another important current task is to determine the possible "points of action" of targeted drugs in the oncogenesis of CP. Thus, it has been demonstrated that Gefitinib (an antitumor drug belonging to the anilino-

**Frequency of studies focused on various tumor growth factors (for CP) in global literature**

| Factor | Number of publications | Greatest number of cases | CP under study | Reference |
|---|---|---|---|---|
| MIB-1/Ki-67 | 8 | 67 | ACP+PCP | [1, 8, 12, 21, 37, 44, 60, 65] |
| Beta-catenin | 6 | 67 | ACP+PCP | [8, 15, 17, 18, 24, 57] |
| p63 | 2 | 67 | ACP+PCP | [8, 35] |
| p53 | 5 | 51 | ACP+PCP | [1, 19, 28, 35, 60] |
| Retinoic acid receptors (RARs) | 2 | 51 | ACP | [28, 33] |
| Galectin-3 | 2 | 51 | ACP | [28, 41] |
| Macrophage-inhibiting factor — MIF | 2 | 51 | ACP | [28, 40] |
| MVD | 3 | 47 | ACP+PCP | [11, 60, 65] |
| CK5/CK8/CK18/CK19 | 1 | 47 | ACP+PCP | [60] |
| Lamin8 | 1 | 47 | ACP+PCP | [60] |
| Carcinoembrionary antigen [CEA] | 1 | 47 | ACP+PCP | [60] |
| Glial fibrillary acidic protein (GFAP) | 1 | 47 | ACP+PCP | [60] |
| Epithelial membrane antigen (EMA) | 1 | 47 | ACP+PCP | [60] |
| Estrogen(ER)/progesterone(PR) receptor | 1 | 43 | Data not available | [21] |
| EGFR EGFR-P | 1 | 25 | ACP | [17] |
| Fascin | 1 | 25 | ACP | [17] |
| CK8, CK20 | 1 | 25 | Data not available | [27] |
| Carbonic anhydrase IX (CA IX) | 1 | 20 | Cystic CP | [43] |
| Enamel proteins | 1 | 16 | ACP+PCP | [58] |
| LEF1 | 1 | 16 | ACP+PCP | [58] |
| DeltaNp63 | 1 | 15 | ACP+PCP | [35] |
| p73 | 1 | 15 | ACP+PCP | [35] |
| CD34 for MVD | 3 | 14 | ACP | [11, 64, 65] |
| Integrin alpha-vbeta-3 | 1 | 14 | ACP | [65] |
| VEG/PF vascular endothelial growth/ permeability factor | 1 | 12 | Data not available | [63] |
| Chromosomal mutations without specifying | 1 | 11 | ACP | [67] |
| Alpha-defensins 1—3 | 1 | 6 | Data not available | [41] |
| Mutations: D32Y, G34R и G34V | 1 | 3 | Data not available | [25] |
| VEGF | 2 | Data not available | ACP | [11, 64] |
| CD105 | 1 | « | ACP | [11] |
| VEGFR-2, mRNA | 1 | « | ACP | [64] |
| Endostatin | 1 | « | ACP | [11] |
| Activating beta-catenin (CTNNB1) mutations | 1 | « | ACP+PCP | [18] |
| Axin-2, BMP4, Exon3, 4, 8—13 | 1 | « | ACP+PCP | [18] |
| Catepsin B, D, K | 1 | « | ACP | [33] |

quinazoline class, which selectively inhibits tyrosine kinase of the epidermal growth factor) reduces the mobility of tumor cells and fascin expression and activates apoptosis. Affecting the EGFR signaling pathway by targeting drugs (such as gefitinib) can be used for drug therapy in patients with CP [17].

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## Commentary

Craniopharyngiomas are tumors of complex structure and histogenesis. Their histological behavior is often unpredictable. From the conventional morphological perspective, craniopharyngiomas exhibit no strongly noticeable signs of neither benign nor malignant potential.

Modern morphology significantly relies on molecular biology and uses this discipline for its development. Nowadays, there are multiple facilities for studying the oncological, morphogenetic, and etiopathological aspects of craniopharyngeal development and behavior at a new level.

The authors of this review have summarized a large body of recent specialized literature on morphology and molecular biology of craniopharyngiomas. An attempt to summarize and systematize the most significant biomarkers among the ones that have been studies was made with allowance for the potential practical significance for diagnosing, prognosing the treatment outcomes, and planning combined therapy. The review focuses on the most significant aspects of the emergence, development, progression, and malignization of craniopharyngiomas.

Attention has also been paid to the current advance and knowledge in the development and histogenesis of two major craniopharyngioma types – adamantinomatous and papillary craniopharyngiomas, which have specific features and are considered to be completely different diseases by some authors (this point of view is reasonable, although disputable as well).

The absence of comprehensive original studies devoted to craniopharyngiomas in Russian literature over the past 10 year could hardly leave the character of this review unaffected. The authors grope for those data and those published results that can be extremely useful for their further research (as well as research conducted by other scientists) devoted to the comprehensive, multi-level, and multi-factor studying of craniopharyngiomas, the mysterious and insufficiently studied group of tumors.

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