Cranioopharyngioma accounts for 5–10% of childhood tumors. Two histological variants are known: adamantinomatous, typically occurring in the pediatric population, and the squamous papillary form, frequent in adults. These histological forms differ in pathological features, reflecting a distinct oncogenetic origin. Adamantinomatous craniopharyngiomas arise from a neoplastic transformation of the epithelial remnants of the craniopharyngeal duct, involuting during embryological development of the adenohypophysis. The squamous papillary variant arises from a metaplastic process involving the adenohypophyseal cells in the pars tuberalis, leading to the formation of squamous cell nests.

Although a purely surgical approach aimed at total resection has been advocated to cure craniopharyngiomas, this management strategy is often burdened by high morbidity because of the critical relationships of this tumor with neighboring vascular and nervous structures. The identification of new therapies would help to comprehend the molecular mechanisms underlying the clinically aggressive behavior of these lesions. Although recent studies have been aimed at clarifying some aspect of neoplastic cell transformation, the molecular pathogenesis of craniopharyngiomas has not been systematically examined in literature. In this paper we attempted to critically review the recent literature on the oncogenetic mechanisms of craniopharyngiomas and their therapeutic implications.

**Molecular Pathogenesis**

The biological mechanisms at the base of the aggressive neoplastic nature of a lesion are as follows: 1) cellular proliferation depending on failure of the apoptotic pathway and activation of the antiapoptotic pathway or on sensitivity to growth factors, 2) cellular anaplasia, 3) local invasiveness, and 4) neoangiogenesis. These features are as strictly interrelated as the molecular mechanisms underlying them. In addition, every neoplastic lesion has another typical skill—namely, elusion of the immune system, which is essential to its existence. In craniopharyngiomas, the role of the immune response is even more complex, as discussed below.

**Cellular Proliferation: Failure of the Apoptotic Pathway and Activation of the Antiapoptotic Pathway**

**Beta-Catenin and Wnt.** Dysregulation of the Wnt signaling pathway could be a molecular mechanism involved in neoplastic cellular transformation. Under physiological conditions, binding of Wnt to a membrane receptor initiates an intracellular signaling cascade resulting in the inactivation of the cytoplasmic glycogen synthase kinase 3β (GSK3beta) complex, including adenomatous polyposis coli, beta-catenin, Axin, and components of...
the ubiquitin ligation machinery. Whereas this proteasomal complex is appointed to beta-catenin degradation, and consequently its inactivation, beta-catenin molecules can translocate into the nucleus, where they interact with members of the T cell factor family of transcription factors.9 Thus, intranuclear beta-catenin accumulation enhances the expression of target genes including c-myc and cyclin D114,15 and plays a fundamental role in proliferation as well as pattern formation, morphogenesis, and the evolution of polarity.

Recently, mutations of the glycogen synthase kinase 3β binding domain of beta-catenin were detected in adamantinomatous craniopharyngioma as well as calcifying odontogenic cysts and pilomatrixoma.13,19,38,39,47 These mutations could cause an aberrant and persistent activation of the pathway cited above, leading to an enhanced expression of Axin2 and bone morphogenetic protein 4 in craniopharyngioma.25 The enhanced expression of Axin can be interpreted as a negative feedback of beta-catenin activity—namely an attempt of the cell to increase production of the component of proteasomal complex appointed to degradation of beta-catenin to decrease its cellular concentration and thus its nuclear activity.

Macrophage Migration Inhibiting Factors and Galectins. Macrophage-inhibiting factor is another molecule probably involved in the oncogenesis of craniopharyngioma. The MIF mRNA and protein are expressed in the normal human epidermis and nerve cells.31,32,41 The influence of MIF has been described in various pathological conditions of the skin, ranging from inflammatory diseases to epidermal hyperplasia.10,40,42 In this context MIF could act as a stimulator of tumor and vessel growth.28,30 In an indirect manner, the role of MIF in tumor cell growth was also demonstrated by evidence that anti-MIF antibodies effectively suppress tumor growth and tumor-associated angiogenesis.20

Under physiological conditions, MIF binds to Jab1 in the cell, which induces the phosphorylation of c-Jun and AP-1 and promotes the degradation of p27Kip1; the result is a reduction in the growth-promoting effects of Jab1.4,20 The MIF expression level seems to correlate with the risk of recurrence in craniopharyngioma, as it was significantly lower in rapidly recurring craniopharyngiomas than in the slowly recurring or nonrecurring lesions.23

Moreover, MIF expression in cholesteatomas correlates with an antiapoptotic endogenous lectin, namely, galectin-3. Indeed, mammalian galectins, which are beta-galactoside–binding proteins, can also exert a notable influence on growth regulation through proapoptotic (for example, galectin-1) or antiapoptotic (for example, galectin-3) mechanisms.9,22,42

Analogous to MIF, galectin-3 levels of expression were significantly lower in rapidly recurrent craniopharyngiomas.23 In view of the antiapoptotic role of galectin-3, its low level of expression in recurring craniopharyngiomas seems to be related more to its role in phagocytosis. In this context the low levels of galectin-3 could correlate the oncogenesis of craniopharyngioma with defects in the normal biological elimination of embryonal tissue remnants.23

Cellular Proliferation: Sensitivity to Growth Factors

The environment in which craniopharyngiomas arise can play an important role, so that close contact with the pituitary gland and the hypothalamus may influence its growth.

Increased expression of mRNAs for estrogen and progesterone receptors has been observed in the proliferative epithelial component of craniopharyngiomas,6 and this message from the cytoplasm would be translated into biologically active receptor protein.16 Moreover, despite the increased expression of mRNA for estrogen receptors, coexpression of the estrogen receptor protein was finally detected on occasion,26 and the correlation with clinical outcome is not clear.

Estrogen and progesterone receptors could be markers of a high tissue differentiating potential, as their coexpression would be associated with a low risk of tumor regrowth.18

Anaplasia: RAR

The correlation of anaplasia with the risk of recurrence is well proved by the expression levels of RAR. Recurrent adamantinomatous craniopharyngiomas are characterized by low levels of RARβ and high levels of RARγ.25 The RARs belong to a major family of biological regulators that drive maturation in different types of epithelia (including the epidermis), as it is well known that the levels of expression of RAR isotypes differ markedly in relation to levels of maturation and/or differentiation of the epidermis.5,36

Invasiveness: Cathepsins

Recent studies have pointed out the role of cathepsins, a class of proteinases acting upstream of metalloproteinases in the proteolytic cascade, enabling tumor cells to invade adjacent normal tissue. Recurrent adamantinomatous craniopharyngiomas are characterized by low levels of cathepsin D and high levels of cathepsin K, and so revealing the same biphasic pattern of expression seen in RAR.25 On the contrary, although the expression of cathepsin B increases during the malignant progression of primary brain tumors and so is considered a significant prognostic factor,44 to date its level has not been shown to be related to the aggressiveness of craniopharyngioma.25

The mechanism acting downstream remains unclear. Cathepsin D secreted from human prostate carcinoma cells is responsible for the generation of angiotatin, a potent endogenous inhibitor of angiogenesis, and this suggests that it contributes to the prevention of tumor growth and the angiogenesis-dependent growth of metastases.48

The level of expression of cathepsin D is significantly higher in more differentiated craniopharyngiomas, showing concomitant high levels of RARβ expression than in craniopharyngiomas with lower levels of RARβ expression.23 The possibility thus remains that, as in the case of human prostate cancer cells, cathepsin D (high in the case of craniopharyngiomas with high levels of RARβ, and so more differentiated) facilitates the generation of angiostatin in craniopharyngiomas and thereby decreases postsurgical regrowth and/or recurrence.
Molecular pathogenesis of craniopharyngioma

On the other hand, cathepsin K is a cysteine protease of the papain family, which can cleave bone proteins such as Type I collagen, osteopontin, and osteonectin. The knockout of cathepsin K in mice leads to retarded bone matrix degradation and osteopetrosis. A high level of cathepsin K was detected in recurrent craniopharyngiomas. Moreover, this finding seems to be related to cellular undifferentiation, represented by a pattern showing low levels of RARβ and high levels of RARγ.

Neoangiogenesis: VEGF

Neoangiogenesis is a limiting factor for tumor growth. Microvessel density, a measure of angiogenesis, has been proposed as a prognostic indicator correlating with an increased risk of recurrence. However, conflicting results on the relationships between microvessel density and the tissue expression of vascularization stimulatory and inhibitory factors (VEGF and endostatin, respectively) could favor a modification able to enhance the neovascularization stimulus at the cytoplasmic level of postreceptor transduction of the signal or at the membrane level—namely, an increased concentration of a receptor such as VEGFR-2. On the other hand, the degree of expression of VEGF seems to play an important role in tumor cyst formation.

Role of Immune System Response: Defensins

After systematic consideration of the molecular mechanisms at the base of the growth of the solid component of craniopharyngiomas, we must specifically discuss cyst formation given that almost 90% of these tumors have a cystic component and that in 60% of cases the cystic portion is predominant. The cystic element is responsible for almost all the symptoms related to mass effect. Moreover, its presence is associated with a major risk of recurrence, and thus suggesting a proliferative mechanism in its genesis and growth.

Much recent research aims to characterize the cyst fluid to understand the mechanism of formation and to define treatments able to reduce cyst volume and inhibit the formation of new cysts. Indeed, the formation mechanism of cystic fluid has always been debated: it could be the result of blood-brain barrier impairment, but surely an active secretory process takes part in its formation. Recently, α-defensins 1–3 have been identified as relevant components of cyst fluid. The presence of these antimicrobial peptides would suggest a possible involvement of the innate immune response in the formation and maintenance of the craniopharyngioma-associated cyst. Indeed, human α-defensins 1–3 constitute 30–50% of the total protein content of neutrophil azurophil granules, with a well-known powerful antibacterial and antiviral activity. The α-defensin expression is significantly increased in the saliva of patients with oral squamous cell carcinomas in the fluid of jaw cysts, and in the plasma of patients with sepsis and meningitis. Moreover, the expression of these peptides decreases as a function of the effectiveness of intracystic IFN-α treatment and so correlates with clinical patient outcome. Authors of future studies should clarify whether the reduction in α-defensins derives from a direct antitumoral effect of IFN-α on squamous epithelial cells of the craniopharyngioma cyst or from its immunomodulatory effects on the recruitment of cells of innate immune systems or whether both action mechanisms are implicated.

Conclusions

The term “craniopharyngioma” refers to “kaleidoscopic tumors, solid and cystic, which take origin from epithelial rests ascribable to an imperfect closure of the hypophysis or craniopharyngeal duct.” In this primordial view, the craniopharyngioma is a mass exerting compression and the distinction between the cystic and solid components is only grossly understood, but the term “kaleidoscopic” let us suppose that Cushing understood the complexity of this tumor. Leading surgeons have devoted their efforts to clarifying the true nature of this tumor, namely, its malignant clinical behavior characterized by local invasiveness and a high rate of recurrence, which is in clear contradiction with its benign histological aspect. We hope that the view of this tumor as a complex molecular disease rather than a simple mass can be the first step in defining the best treatment.

Initial efforts have been focused on correlating the mitotic activity of craniopharyngioma with its clinical behavior, unfortunately producing conflicting results. These contradictions can be clarified by the current evolution from the “microscopic” view to the “molecular” view. In fact, at the molecular level the cellular proliferation results in multiple failures of the apoptotic pathway combined with persistent activation of the antiapoptotic pathway. The identification of the impaired stages of this circuitry could explain the difference in the incidence of recurrence despite similar mitotic activity.

Besides the cellular proliferation, other cellular physiological functions became abnormal as a result of the neoplastic transformation, and so affected the clinical behavior of craniopharyngioma. Therefore, the terms of the matter are even more complex.

Nowadays, advances in our knowledge of oncogenic mechanisms would lead us to identify critical checkpoints in tumor cell transformation, to drive the definition of specific therapeutic agents able to reverse the neoplastic process at these levels. In this context, this biological approach aims to defeat the tumor by “curing” only the abnormal neoplastic cell. An example of this new approach is the reactivation of the apoptotic pathway—that is, a physiological mechanism in the normal cell that is eluded by the neoplastic cell—as a result of treatment with intracystic IFN-α.

The final target of this research will be the definition of a tailored therapy combining higher efficacy and safety with lower morbidity. This biological therapy would probably be based on multiple inhibitions that so far have been proved to be more efficient than a single-step inhibition in the treatment of different tumors. On the other hand, considering the immediate future, the definition of molecular markers of malignancy will allow us to stratify patients harboring a craniopharyngioma on the basis of...
its biological aggressiveness, and consequently enabling the surgeon to modulate treatment intensity.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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