PROGRESSES IN THE UNDERSTANDING OF THE PATHOGENESIS OF CRANIOPHARYNGIOMAS

C. Capatina*

“Carol Davila” University, Dept. of Endocrinology, “C.I. Parhon” National Institute of Endocrinology, Bucharest, Romania

Abstract

Craniopharyngiomas (CP) are rare, dysembryoplastic tumors of the hypothalamo-pituitary area. There are two very distinct pathological types: adamantinomatous (ACP) and papillary (PCP). ACP and PCP also have significant clinical differences, pointing to a different pathogenesis. This only began to be elucidated lately and indeed discovered specific, mutually exclusive mutations with pathogenetic role in ACP and PCP, respectively.

The vast majority of ACP harbor an activating mutation of the CTNNB1 gene coding for β -catenin (member of the Wnt pathway). The mutation was proved to be pathogenetic in animal models and a tumorigenesis model has already been created.

In contrast, in PCP, BRAF (gene coding for a main actor in the MAPkinase pathway) mutations have been found in the majority of cases.

These findings can improve the differential diagnosis of intracranial tumors (by specifically designed immunohistochemistry-antibodies) and the design of molecules to inhibit the disordered intracellular pathways. Such molecules are already available and promising for the BRAF/MAPkinase pathway.

In conclusion, extremely significant progresses have been made in revealing the complex process of tumorigenesis in CP and they are likely to solve in the foreseeable future many challenges we typically face in the clear positive diagnosis and optimal management of these rare tumors.

Key words: craniopharyngiomas, papillary, adamantinomatous, pathogenesis, genetic mutations.

Craniopharyngiomas (CP) are rare tumors, frequently sporadic and only recently significant insight into their pathogenesis has been gained using advanced molecular genetics tools.

Pathologically two distinct types of CP are described. The adamantinomatous craniopharyngioma

(ACP) occurs more frequently in childhood onset cases. ACPs are frequently calcified tumors with possible intrasellar component, macroscopically having a lobulated aspect and frequent cystic components. The papillary form (PCP) occurs almost exclusively in adults. PCPs are usually suprasellar, predominantly solid, with only rare calcifications (1). These striking differences suggest that different pathogenetical mechanisms might also be involved in the tumorigenesis of ACP and PCP, respectively.

The interest in elucidating the genetical basis of CP is relatively recent, explained by the fact that most cases occur sporadically, while cases with familial aggregation are exceptional. Initial studies assessing possible chromosomal abnormalities or some candidate-genes (eg those involved in odontogenic lesions, with histological similarities to CP, or those coding for protein G subunits) offered negative results (1). Since a minority of CP were proved to be monoclonal tumors (2), further studies to investigate possible genetic defects have been pursued.

Unexpected results came from the investigation of the Wnt pathway (an essential pathway for cell proliferation and differentiation, of maximum importance during pituitary organogenesis). The CTNNB1 gene, coding for β -catenin (a protein of the Wnt pathway, involved in cell-cell adhesion), has been shown to harbor a mutation in 90% of ACP cases. These mutations transform the β -catenin protein (normally located at the cell membrane level) in such a way that it migrates within the cytoplasm and cell nucleus leading to the activation of the Wnt pathway (maintained inactive under normal conditions).

Immunohistochemical analysis with antibodies for β -catenin revealed significant differences between ACP (frequently harboring mutations of the coding gene) and PCP. In ACP the mutated β -catenin is localized in the cytoplasm and nucleus while in PCP it

*Correspondence to: Cristina Capatina MD, “Carol Davila” University, Department of Endocrinology, 34-36 Aviatorilor blvd., Bucharest, 011863, Romania, E-mail: cristina.capatina@yahoo.com

can be observed only at the cell membrane. This marker can be successfully used in the differential diagnosis of sellar region tumors, in order to certify a diagnosis of ACP (3).

A murine model of ACP was later designed in order to prove the etiologic role of the β -catenin mutation. (4) This also led to the clarification of the paracrine model of tumorigenesis. Inducing β -catenin mutations in cells with characteristic of stem cell (SOX 2 positive cells; but not in other cells) led to the clustering of the cells harboring the mutation and eventually the development of a tumor with definite ACP characteristics. Intriguingly, the tumor cells were not derived from the SOX 2 positive cells, demonstrating significant paracrine signalling between the precursor cells harboring the mutation and the neighbouring cells (4-6). The role of the factors involved is still to be revealed. Also, numerous questions still remain unanswered regarding the intermediate steps and additional molecular factors, the mechanism of cyst formation in CP, the precursor cell responsible for tumorigenesis in adult-onset cases etc. (4, 7).

Other pathways seem to be involved in ACP pathogenesis eg. the SHH (sonic hedgehog-overexpressed in clustered ACP cells), EGF receptor pathway (phosphorylated EGFR in clustered ACP cells)- reviewed in (7). Further research is needed and hopefully will shed more light on the complexity of the phenomena.

The possible inhibition of β -catenin (with therapeutic potential in ACP) is an active research area. No molecule acting on this pathway is available yet. One isolated report suggested, rather surprisingly, that the use of indomethacin or sulindac (commonly used AINS drugs) inhibited tumor growth in vitro and in vivo on the murine model of ACP (8).

For PCP, the vast majority of tumors harbor BRAF mutations (BRAF is an essential step in the MAPK pathway, involved in cell proliferation, differentiation and survival as well as angiogenesis) (1).

A mutation-specific antibody (VE1), recognizing only the protein resulting from the mutant gene has also been designed. Its use could improve the pathological diagnosis of PCP (9). There was a good concordance between the immunohistochemical analysis using the VE1 antibody and the genetic diagnosis (10). However, the VE1 antibody cross-reacts with certain normal tissues, so the technique needs to be refined before eventually being of clinical use (11).

Also, in contrast to ACP and the Wnt pathway, inhibitors of the BRAF-MAPK pathway have already

been designed and are available (as this pathway is altered in numerous other human diseases). The therapeutic use of these agents in PCP is limited to case reports, mainly due to the rarity of the disease. Thus, the activated BRAF protein can be inhibited by already available drugs (vemurafenib, dabrafenib) while the activated MEK is inhibited by trametinib or selumetinib. Some of these agents inhibiting the BRAF (eg dabrafenib) and MEK pathways (eg trametinib) have led to the significant decrease of tumor volume and Ki67 index in isolated published PCP cases (12). Other BRAF inhibitors, already used with good results in certain malignancies (such as hairy cell leukemia or melanoma) are yet to be tested.

All these significant progresses open new exciting perspectives for the treatment of these rare and challenging tumors. Molecules inhibiting the pathways with pathogenetic role in CP are to be further tested and new molecules will probably emerge in the future. The immunohistochemical analysis using specific antibodies to detect the mutant proteins in each type of CP could become part of the routine pathological diagnosis (easier to perform and cheaper than the genetical analysis of each case), helping to direct the patient to the most adequate medical treatment or clinical trial. We can also look forward to a time when efficient medical treatment will be available and current therapeutic methods (surgery and radiotherapy, both with relatively limited results and/or frequent adverse reactions) could remain second-line treatments, reserved for the most severe cases, unresponsive to medical treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Hage M, Lombes M, Chanson P. Craniopharyngiomas: progress in pathogenesis and therapeutics. *Ann Endocrinol (Paris)*. 2014;75 Suppl 1(S46-S54).
2. Sarubi JC, Bei H, Adams EF, Boson WL, Friedman E, Brandao K, Kalapothakis E, Miranda D, Valle FL, Sarquis MS, De Marco L. Clonal composition of human adamantinomatous craniopharyngiomas and somatic mutation analyses of the patched (PTCH), Gsalpha and Gi2alpha genes. *Neurosci Lett*. 2001;310(1):5-8.
3. Preda V, Larkin SJ, Karavitaki N, Ansorge O, and Grossman AB. The Wnt signalling cascade and the adherens junction complex in craniopharyngioma tumorigenesis. *Endocr Pathol*. 2015;26(1):1-8.
4. Andoniadou CL, Gaston-Massuet C, Reddy R, Schneider RP, Blasco MA, Le Tissier P, Jacques TS, Pevny LH, Dattani MT, Martinez-Barbera JP. Identification of novel pathways involved in the pathogenesis of human adamantinomatous craniopharyngioma. *Acta Neuropathol*. 2012;124(2):259-271.

5. Martinez-Barbera JP, Andoniadou CL. Concise Review: Paracrine Role of Stem Cells in Pituitary Tumors: A Focus on Adamantinomatous Craniopharyngioma. *Stem Cells*. 2016;34(2):268-276.
6. Andoniadou CL, Matsushima D, Mousavy Gharavy SN, Signore M, Mackintosh AI, Schaeffer M, Gaston-Massuet C, Mollard P, Jacques TS, Le Tissier P, Dattani MT, Pevny LH, Martinez-Barbera JP. Sox2(+) stem/progenitor cells in the adult mouse pituitary support organ homeostasis and have tumor-inducing potential. *Cell Stem Cell*. 2013;13(4):433-445.
7. Apps JR, and Martinez-Barbera JP. Molecular pathology of adamantinomatous craniopharyngioma: review and opportunities for practice. *Neurosurg Focus*. 2016;41(6):E4.
8. Gaston-Massuet C. ICE/ENDO. Chicago, USA; 2014.
9. Schweizer L, Capper D, Holsken A, Fahlbusch R, Flitsch J, Buchfelder M, Herold-Mende C, von Deimling A, and Buslei R. BRAF V600E analysis for the differentiation of papillary craniopharyngiomas and Rathke's cleft cysts. *Neuropathol Appl Neurobiol*. 2015;41(6):733-742.
10. Brastianos PK, Taylor-Weiner A, Manley PE, Jones RT, Dias-Santagata D, Thorner AR, Lawrence MS, Rodriguez FJ, Bernardo LA, Schubert L, Sunkavalli A, Shillingford N, Calicchio ML, Lidov HG, Taha H, Martinez-Lage M, Santi M, Storm PB, Lee JY, Palmer JN, Adappa ND, Scott RM, Dunn IF, Laws ER Jr, Stewart C, Ligon KL, Hoang MP, Van Hummelen P, Hahn WC, Louis DN, Resnick AC, Kieran MW, Getz G, Santagata S. Exome sequencing identifies BRAF mutations in papillary craniopharyngiomas. *Nat Genet*. 2014;46(2):161-165.
11. Brastianos PK, and Santagata S. Endocrine tumors: BRAF V600E mutations in papillary craniopharyngioma. *Eur J Endocrinol*. 2016;174(4):R139-144.
12. Brastianos PK, Shankar GM, Gill CM, Taylor-Weiner A, Nayyar N, Panka DJ, Sullivan RJ, Frederick DT, Abedalthagafi M, Jones PS, Dunn IF, Nahed BV, Romero JM, Louis DN, Getz G, Cahill DP, Santagata S, Curry WT Jr, Barker FG 2nd. Dramatic Response of BRAF V600E Mutant Papillary Craniopharyngioma to Targeted Therapy. *J Natl Cancer Inst*. 2016;108(2).