Role of Dkk-3 and claudin-5 in the neoplastic progression of meningiomas.

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Meningiomas are the most common tumors of the CNS, where the incidence is around 25% of all primary brain tumors (Caruso et al., 2015). The optimal treatment is total resection with removal of the dura mater and bone when infiltrated. Meningiomas may recur after total surgical resection. The histological grading is the most important prognostic factor. WHO grade I meningiomas show a recurrence rate between 7-25%. Atypical meningiomas (WHO grade II) between 29-52%. Anaplastic meningiomas (WHO grade III) between 50-94%. From recent studies the Wnt pathway is emerging as involving in growth and progression of meningioma (Domingues et al., 2015). However, molecular mechanism driving meningioma invasion are not completely clarified. The gene Dkk-3 (Dickkopf WNT signaling pathway inhibitor 3) encodes one of Dickkopf-related protein family of proteins. The activity of this gene is a tumor-suppressive type. The Dkk-3 protein (Dickkopf-related protein 3) is involved in embryonic development through its interactions with the WNT (Foltz et al., 2010). The REIC/Dkk-3 expression has been shown to be down-regulated in various cancer cell lines.

The claudin-5, is an integral membrane protein, which regulate the permeability of the blood-brain barrier. In various pathological processes, including inflammation, trauma and tumor, claudin 5 regulate the change in endothelial or epithelial perme¬ability (Jia et al., 2014), therefore, modification in claudin-5 expression may play a role in malignant transformation.

Aim of our study was to study the role of Dkk-3 expression and claudin-5 in meningiomas of different histotype and histological grade.

We evaluated how meningiomas modify DKK-3 expression in 30 tumors biopsies assessing both immunohistochemistry and western blotting. The tissue samples were embedded in paraffin for immunohistochemical analysis. The expression strength was analyzed and graded based on the positive ratio and intensity of immunoreactivity. The molecular analyses were performed on frozen sections of tumor tissue by Western Blot method. Statistical analysis was also performed.

The expression of Dkk-3 protein and claudin-5 were significantly reduced in meningioma samples compared to control tissue. These results were confirmed by immunohistochemistry that reveals a slight expression of Dkk-3 protein in meningioma samples examined. It was also highlighted an irregular positivity of claudin-5 protein, on vascular localization. Claudin-5 levels were inversely regulated in meningiomas proteic extract with decreased levels compared to controls.

Overexpression of Dkk-3 has been shown to mediate potent anti-tumor effects including reduced cell proliferation, independent growth, invasion and metastasis, and induced cancer cell specific apoptosis. Our preliminary results can suggest that in meningiomas Dkk-3 and Claudin-5 are downregulated. There is an alteration of the BBB and a decreasing of apoptotic susceptibility. The immunoreactivity of vascular neoplastic endothelium can suggest a role in angiogenesis. We

suggest that the re-establishment of Dkk-3 and claudin-5 level can represent a new potential therapeutic approach in meningiomas treatment also by modulation of blood-brain barrier permeability.

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