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INVOLVEMENT OF N-, E-CADHERIN AND BETA-CATENIN IN PROGRESSION OF INTRACRANIAL MENINGIOMA

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The majority of intracranial meningiomas are benign primary tumors. However, 20% are classified as atypical (grade II) and anaplastic (grade III) showing aggressive character and higher probability of recurrence. We believe that such an invasive character of meningioma subtypes could be explained due to the epithelial-mesenchymal transition (EMT) and the activation of canonical Wnt signaling pathway. The malfunctioning of Wnt signaling has been found in many human tumors and many key molecules of Wnt pathway are also involved in EMT. EMT is a biological process necessary for tumor invasion, during which cells undergo molecular changes, become motile and metastasize. During EMT, cells show the so called "cadherin switch" which is characterized by loss of expression of E-cadherin - protein marker of epithelial cells, and by increased expression of N-cadherin followed by the acquisition of mesenchymal phenotype. Therefore, the aim of this study was to investigate if main actors of EMT and canonical Wnt signaling pathway are affected in progression of intracranial meningiomas and to identify potential markers for the control of cellular mobility. In order to do so, we analyzed protein expression and localization of N-cadherin, E-cadherin and beta-catenin in 50 samples of human meningioma with different grades of malignancy. Expression and localization of proteins was investigated using DAB-labeled immunohistochemistry (EnVisionTM, Dako REALTM) and specific monoclonal antibodies for N-cadherin, E-cadherin and beta-catenin on paraffin-embedded meningioma sections. Image analysis (ImageJ – NIH, NCI, Bethesda MD, USA) was also used. For the purpose of identifying the subcellular localization and levels of expression, 200 cells of tumor hot spots were selected and counted. Also, we tested if the expression of E-cadherin protein was influenced by genetic alternations of its CDH1 gene. This was studied by polymerase chain reaction (PCR)/ loss of heterozygosity (LOH) or microsatellite instability (MSI) analyses using microsatellite marker D16S3025. Our results demonstrated that the majority of meningioma samples (70%) showed moderate expression levels of N-cadherin. Beta-catenin was upregulated and transferred to the nucleus in 71.2% of meningiomas which is indicative of the pathway activation. The results on CDH1 genetic changes showed that 9% of meningiomas harbored LOH, 13% showed MSI and 4% of them showed both LOH and MSI. In patients who demonstrated CDH1 genetic changes moderate expression levels of E-cadherin protein were observed. The higher percent of observed MSI could be explained by our previous study (Pećina-Šlaus et al., Tumour Biol. 2017; 39(7):1010428317705791.) where we showed constant presence of MSI and alterations of mismatch repair genes MLH1 and MSH2 in our collection of meningioma patients. After additional future analyses our findings could be useful as potential biomarkers of cellular mobility of invasive intracranial meningiomas.

BIOGRAPHY

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