25. UNRAVELING THE MOLECULAR SIGNALING PATHWAYS IN GLIAL TUMORS WITH METHYLATED MGMT PROMOTERS

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Introduction. Most gliomas are typically assessed using imaging methods. A recent advancement in this regard involves the integration of biomarkers in conjunction with imaging techniques, such as 18F-FDG-PET-based radiomics for evaluating the methylation status of the MGMT promoter and relaxation-compensated multipool CEST MRI for assessing the mutation status of the IDH gene. The MGMT gene is situated on the 10q26 chromosome band. Its promoter lacks the TATA and CAT boxes, similar to other housekeeping genes. MGMT status can be determined through either a biopsy or by examining the DNA present in circulating extracellular vesicles (EVs) in the bloodstream. Methylation-specific PCR (MSP) is the preferred method for identifying DNA polymorphisms in the MGMT promoter.

Aim of study. To elucidate the biochemical mechanisms underlying chemotherapy susceptibility in patients with MGMT promoter methylation.

Methods and materials. After entering the keywords 'biochemical pathways in MGMT methylated glioma' into the PubMed database were retrieved a total of 1,255 results. Following a thorough review of the initial 100 sources, 37 of them were deemed relevant and considered for further analysis.

Results. O6-methylguanine-DNA methyltransferase (MGMT), often referred to as the, plays a pivotal role in repairing O6-guanine lesions in gliomas. Chemotherapeutic agents like temozolomide (TMZ), temozolomide/lomustine (TMZ/CCNU), bevacizumab/irinotecan (BEV/IRI), and enzastaurin induce cytotoxic lesions on O6-guanine, N7-guanine, and N3-adenine. Methylation of the MGMT promoter plays a crucial role in increasing susceptibility to the aforementioned chemotherapeutics in glioma treatment. An exception to this principle is observed in gliosarcomas, gray zone tumours (comprising alternating methylated/unmethylated cells) and among the patients in specific geographic regions, such as Spain. Notably, the methylation of the MGMT promoter and its expression are not influenced by a person's race. The explanation for population-based independence of MGMT promoter methylation status lies in the polymorphism of other housekeeping genes (XAF1, AEBP1, MTHFR, IFT25, HMGA2) that protect the glioma stem cells from apoptosis.

Conclusion. The MGMT promoter methylation status serves as a relative prognostic marker, as it does not apply universally to the more complex forms of gliomas. The typical glioma types have a linear correlation of survival in means of the number of methylations in the promoter region of the MGMT gene.

Keywords. O6-methylguanine-DNA-methyltransferase, gliomas, marker