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Clinical diagnostic utility of *MGMT* promoter methylation

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Abstract

Tumor suppressor genes and DNA repair genes can be inactivated not only by genetic lesions, like mutations or deletions, but also by aberrant DNA methylation of promoter regions. These DNA methylation alterations may serve as biomarkers for early detection, refinement of diagnosis, prognosis, or prediction of therapy response. Despite a long history of DNA methylation research in the field of oncology so far only very few aberrant DNA methylation events are of proven and generally accepted clinical value and are part of the routine diagnostic work-up of cancer patient samples. Hypermethylation of the *MGMT* gene promoter in glioblastoma is one of the very few DNA methylation biomarkers that has entered routine clinical diagnostics. In this very aggressive primary brain tumor it is associated with an overall better prognosis and a better response to alkylating therapy. This narrative review provides an overview about the underlying biology, the methodological challenges, and the clinical utility of *MGMT* promoter methylation, primarily in the context of glioblastoma. Emerging applications in other cancer types are also summarized and discussed. Throughout the review the focus is more on a critical discussion of concepts and relevant publications and their merits and shortcomings than trying to achieve complete coverage of the voluminous literature.

Keywords: DNA methylation; MGMT gene; biomarker; glioblastoma; prediction; prognosis.

Plain language summary

DNA methylation is a modification of the genetic material (the chromosomes) that can influence the activity of genes. Thus, it indicates how cells will respond to external stimuli and changing conditions in the cellular environment. In cancer tissues, DNA methylation can determine whether and how cancer cells react to chemotherapy. Brain tumors are a very aggressive class of human cancers that unfortunately often come with a quite limited life expectancy for the affected patients. If the gene encoding the DNA repair enzyme called "*MGMT*" is switched off by DNA methylation, the tumors react more favorably to certain chemotherapeutic agents, resulting in a longer survival of the patients. Recent studies suggest that this might also be true for other malignancies.There are many different methods used to figure out whether a certain gene is affected by DNA methylation, some of which are still under development. This makes the comparison of different studies using different methodologies quite challenging and requires detailed technical know-how in order to evaluate DNA methylation detection assays properly and select the most suitable one.For the coming years an

improvement of the technology together with an international standardization and application to cancer types other than brain tumors is expected.

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