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The role of DNA methylation in directing treatment in medulloblastoma

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Abstract

Medulloblastoma is the most common malignant childhood brain tumor. The disease exhibits significant clinical and molecular heterogeneity which leads to significant differences in outcome. Although survival rates have improved in recent years, outcome for patients with high-risk disease remains poor and survival is associated with significant treatment associated morbidity. Traditional risk stratification was established largely on the basis of clinical and histological factors, but these are not sufficient to capture the full biologic complexity of the disease. Recent advances have underscored the role of DNA methylation as a powerful epigenetic biomarker for precise subgroup stratification and prognostic classification of medulloblastoma into four primary molecular subtypes: WNT, SHH, Group 3, and Group 4. This review summarizes mechanisms of DNA methylation in cancer biology, methylation profiling analytical approaches, and their application in delineating medulloblastoma subtypes. Specific attention is placed on the clinical utility of methylation-based classifiers for guiding therapeutic decisions and clinical trial design.

Keywords: DNA methylation; Medulloblastoma; biomarkers; epigenetics; molecular subgrouping.

Plain language summary

Medulloblastoma is the most common brain cancer in children. Survival rates have improved in recent years, but it remains one of the main causes of death from childhood cancer. Medulloblastoma was initially thought of as a single disease, but more detailed analysis revealed it could be split into four subgroups. These subgroups, called WNT, SHH, Group 3 and Group 4, were found to have different features and result in different outcomes. For example, WNT tumors have the best outcome with survival rates greater than 90%, while patients with group 3 tumors only have about 60% survival. As a result, individual treatment plans can be altered for patients depending on which subgroup they fall into. This means that patients with higher risk can be given more intensive treatments to improve survival, while patients with lower risk can have reduced intensity treatment. This reduced treatment leads to less toxicity and fewer long-term health problems for survivors. More recently, even more detailed analysis has allowed even the four subgroups to be further split into 14 subtypes. These new subtypes are now being included in new clinical trials to allow even greater levels of personalized treatments to ensure that each patient gets the therapies that are best for their specific disease. It is hope that this increase in personalized treatment will lead to further increases in patient survival.