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REVIEW

TRANSITIONING FROM GENOTYPES TO EPIGENOTYPES: WHY THE TIME HAS COME FOR MEDULLOBLASTOMA EPIGENOMICS

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Abstract—Recent advances in genomic technologies have allowed for tremendous progress in our understanding of the biology underlying medulloblastoma, a malignant childhood brain tumor. Consensus molecular subgroups have been put forth by the pediatric neuro-oncology community and next-generation genomic studies have led to an improved description of driver genes and pathways somatically altered in these subgroups. In contrast to the impressive pace at which advances have been made at the level of the medulloblastoma genome, comparable studies of the epigenome have lagged behind. Complementary data yielded from genomic sequencing and copy number profiling have verified frequent targeting of chromatin modifiers in medulloblastoma, highly suggestive of prominent epigenetic deregulation in the disease. Past studies of DNA methylation-dependent gene silencing and microRNA expression analyses further support the concept of medulloblastoma as an epigenetic disease. In this Review, we aim to summarize the key findings of past reports pertaining to medulloblastoma epigenetics as well as recent and ongoing genomic efforts linking somatic alterations of the genome with inferred deregulation of the epigenome. In addition, we predict what is on the horizon for medulloblastoma epigenetics and how aberrant changes in the medulloblastoma epigenome might serve as an attractive target for future therapies.

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Key words: medulloblastoma, epigenomics, chromatin, DNA methylation, neuro-oncology.

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INTRODUCTION

Medulloblastoma is a small round blue cell tumor of the cerebellum that constitutes one of the most common malignant brain tumors of childhood. Overall survival rates range from 60% to 80%, although long-term survivors often face significant treatment-related morbidity secondary to current treatment approaches involving surgical resection, cranio-spinal radiation (children older than 3 years), and chemotherapy. To overcome the significant complications and reduced quality of life associated with conventional treatment for medulloblastoma, a considerable amount of research interest is currently aimed at dissecting the molecular genetics underlying the disease, so that rational targeted therapies can be implemented in an analogous manner to those being used to treat childhood leukemia (Mackall, 2011).

Significant progress has been made in the realm of medulloblastoma genomics during the past few years, especially owing to the rapid evolution in both

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Abbreviations: 5-Aza, 5-aza-2′deoxycytidine; BET, bromodomain and extraterminal; DZNep, 3-Deazaneplanocin A; FFPE, formalin-fixed paraffin embedded; H3K9, histone 3 lysine 9; HATs, histone lysine acetyltransferases; HDAC, histone deacetylase; HDMs, histone lysine demethylases; HGF, hepatocyte growth factor; HMTs, histone lysine methyltransferases; IHC, immunohistochemistry; MAGIC, Medulloblastoma Advanced Genomics International Consortium; N-CoR, nuclear co-receptor; NGS, next-generation sequencing; PCR, polymerase chain reaction; PRC2, Polycomb repressive complex 2; SCNA, Somatic copy number aberrations; WES, whole exome sequencing; WGS, whole genome sequencing; WGBS, whole genome bisulfite sequencing.

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microarray and sequencing technologies making it feasible to study the cancer genome at an unprecedented resolution (Northcott et al., 2010, 2012b). Gene expression array profiling of large cohorts of medulloblastoma specimens has led to the discovery of at least four discrete molecular subgroups: WNT (Wingless), SHH (Sonic hedgehog), Group 3, and Group 4 (Thompson et al., 2006; Kool et al., 2008; Cho et al., 2011; Northcott et al., 2011; Remke et al., 2011a). These subgroups exhibit highly distinct transcriptional and genetic profiles, patient demographics, and clinical behavior (Kool et al., 2012; Northcott et al., 2012a,c). Whether or not each medulloblastoma subgroup arises from a distinct cell-of-origin is currently an area of active investigation. Regardless of their origins, it is now widely accepted that these subgroups represent distinct molecular entities, and future treatment of medulloblastoma, especially molecularly targeted therapies, should take patient subgroup status into account (Northcott et al., 2012c; Taylor et al., 2012).

Recent whole exome and whole genome sequencing (WES and WGS, respectively) studies have provided new insight into the somatically altered genes functioning as 'drivers' in medulloblastoma subgroups (Northcott et al., 2012b). In addition to the known medulloblastoma oncogenes and tumor suppressors, a broad series of novel candidate genes have also been uncovered. The prevalence of somatic alterations (including base-pair level mutations and copy number aberrations) affecting chromatin-modifying genes has been an unexpected finding that has implicated deregulation of the epigenome as an important step during medulloblastoma pathogenesis (Jones et al., 2013). In spite of a few prior reports describing epigenetic silencing of tumor suppressor genes by aberrant promoter methylation, an appreciation for the overall role of epigenetics in medulloblastoma is still just coming to light.

In this Review, we aim to recount the brief history of epigenetic studies of medulloblastoma, including those focused on DNA methylation, microRNAs (miRNAs), and the histone code (Fig. 1). We highlight key findings that have emerged through next-generation genomics, and anticipate what is on the horizon with respect to epigenome-wide surveys of medulloblastoma and the prospect of epigenetic therapies for treatment of the disease.

PAST

Gene silencing by aberrant methylation of CpG islands

Initial clues that suggested a possible role for aberrant epigenetics in medulloblastoma date back more than a

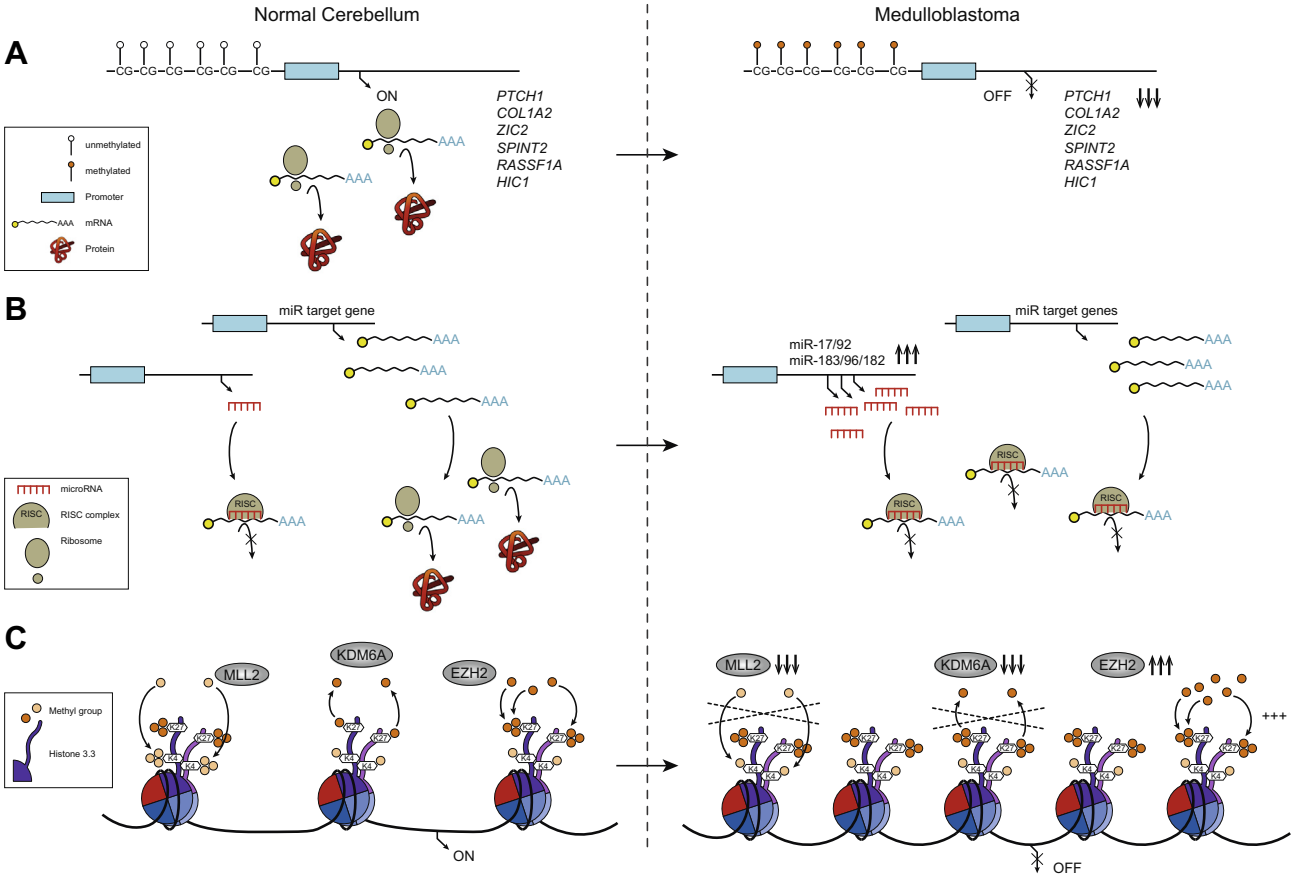

Fig. 1. Overview of epigenetic mechanisms implicated in medulloblastoma. Schematic representation of gene regulation by epigenetics in the normal cerebellum (left side) and in medulloblastoma (right side). (a) Silencing of medulloblastoma tumor suppressor gene expression by promoter hypermethylation. (b) Aberrant expression of oncogenic miRNAs in medulloblastoma. (c) Deregulation of histone 3 lysine 4 (K4) and lysine 27 (K27) methylation states secondary to defects in histone modifying enzymes in medulloblastoma.