Abstract

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"Oncohistones: Exquisite Opportunities and Therapeutic Vulnerabilities"

Brain tumours are the leading cause of cancer related mortality and morbidity in children and young adults. High grade gliomas (HGG) are a particularly lethal and disabling, with barely 10% of children and young adults surviving 3 years after their diagnosis, regardless of enormous efforts to achieve Zingly similar histology. Our landmark discoveries, the foundation of the 2016 World Health Organization (WHO) classification, showed that epigenetic deregulation during brain development is at the core of these cancers. We were the first to identify high-frequency recurrent, gain-of-function, somatic mutations at specific residues in histone 3 (H3) variants in HGG affecting children and young adults. The two mutations found in HGG lead to amino acid changes in key residues of H3 variants: K27M in one of the genes H3F3A/H3.3, HIST1H3B or HIST1H3C/H3.1 occurs in 80% of HGG in the brain midline, including the deadly diffuse intrinsic pontine gliomas; G34V or G34R in H3F3A/H3.3 occurs in 36% of HGG in the cerebral hemispheres. These "oncohistones" are the pediatric counterpart of the recurrent mutations in isocitrate dehydrogenase enzymes (IDH) identified in young adult gliomas, which we now know indirectly affect these histone marks. We uncovered mutations in SETD2, a H3K36 trimethyltransferase, in HGG of the cortex and further showed that K27M and G34R/V H3 mutations are tightly correlated with a distinct global DNA methylation pattern and have neuroanatomical specificity. Indeed, H3K27M specify

brain midline gliomas, while alterations directly or indirectly affecting the K36 mark (SETD2, H3.3G34R/V) chart HGG of the cerebral hemispheres. Each H3 variant has selective, age, and spatial clustering of associated molecular alterations, including mutations in the chromatin remodeller ATRX. We will present our recent findings which indicate that these mutations stall differentiation and block the cell in an undifferentiated state. This “Peter Pan” effect (as we named it) will be discussed as well as how it impacts the epigenome to promote tumorigenesis with the obligate associated genetic alterations we identified in HGG. We will show oncohistones in other non-pediatric cancers and reveal how efforts to model these mutations in isogenic tumour systems, mouse, or fly models are helping identify exquisite therapeutic vulnerabilities. Oncohistones promote an aberrant epigenetic landscape that can be manipulated to the advantage of patients and our efforts to dissect the epigenome in these tumours may provide viable therapeutic strategies in untreatable deadly diseases.