MILESTONE 10

Oncohistones: epigenetic drivers of cancer

Oncogenesis is often a slow process associated with the progressive accumulation of a complex network of genetic alterations, which, over time, dysregulate cellular proliferation and function. However, this aetiology is not the case for paediatric cancers—the discovery of recurrent histone mutations in children with cancer revealed that 'oncohistones' can have vast effects on gene expression and are the root causes of many aggressive paediatric cancers.

As essential components of chromatin, the core histones H2A, H2B, H3 and H4 not only create a structural backbone for eukaryotic DNA packaging, but are also crucial to the regulation of RNA replication, transcription and repair. The roles of histones in these cellular processes are regulated by their patterns of post-translational modifications, such as methylation or acetylation, and therefore depend on the activity of histone-modifying and chromatin-remodelling enzymes.

In 2012, two seminal studies revealed the presence of high-frequency somatic alterations in paediatric high-grade gliomas, including glioblastomas (GBMs). These mutations mainly affected the histone H3 genes *H3-3A* (encoding the histone variant H3.3) and *H3C2* (encoding the canonical histone H3.1). Further studies confirmed that certain paediatric tumours often contain heterozygous missense mutations in H3 genes that do not cause early protein termination and loss, but instead result in gain-of-function changes that drive oncogenesis. These amino acid substitutions often occur in the highly conserved amino terminus of H3, specifically at amino acids K27, K36 and G34, which are associated with post-translational modification of H3. These findings suggest that oncohistones promote tumour initiation and progression by interfering with the regulation of transcription through changes in chromatin remodelling and accessibility.

In 2013, multiple studies reported that the H3 K27M oncohistone leads to a decrease in trimethylated H3K27 (H3K27me3)—a transcriptional repressor—by inhibiting the methyltransferase EZH2, the catalytic subunit of Polycomb enzyme repressive complex 2 (PRC2). Interestingly, residual PRC2 activity is required for tumour proliferation, and EZH2 inhibition has therefore been proposed as a therapeutic target. The loss of H3K27me3 has been associated with the upregulation of many genes involved in developmental neurogenesis.

In 2012, H3 G34R substitutions were also identified as recurrent GBM alterations. A subsequent study suggested that these oncohistones alter the interaction of H3K36me3 with its binding partners, thus leading to the upregulation of the *MYCN* oncogene, and G34R inhibition of KDM4 demethylases has also been reported. Moreover, H3 K36M alterations, which have been identified in chrondroblastomas and sarcomas, can inhibit several H3K36 methyltransferases. The consequent decrease in H3K36me was associated with an increase in H3K27me, which affected the activity of PRC1 complexes and led to the expression of genes known to block mesenchymal differentiation, thus potentially contributing to sarcoma development.

Notably, these different sets of oncohistone amino acid substitutions and the genes that they affect are specifically associated with distinct tumour types and anatomical locations. For example, whereas tumours with K27 alterations often occur in the pons and thalamus, G34 alterations are usually found in tumours that develop in the cerebral hemispheres. Moreover, despite the overall decrease in methylated K27 in tumours with K27M alterations, a 2017 report suggested that some loci (such as *CDKN2A*) retain H3K27me3, thereby leading to a selective gene-silencing programme that promotes oncogenesis while retaining the identity of the tumour cell of origin. Anatomical specificity might be explained by the differential gene expression patterns of canonical and variant H3 genes across different cell types. The expression of canonical histones is restricted to the DNA-replication phase of the cell cycle, whereas histone variants can be expressed throughout any phase of the cell cycle and progressively accumulate in long-lived cells. In addition, canonical H3.1 is dispersed through the genome, whereas the H3.3 variant is incorporated into distinct genomic regions, such as areas of active transcription or regulatory regions. Interestingly, a recent study of patient-derived glioma cell lines has suggested that H3 K27M-mediated loss of H3K27me3 might occur only when oncohistones are incorporated into the chromatin of dividing cells.

A 2019 report suggested that oncohistones might not be restricted to gliomas and sarcomas. Somatic alterations in all core histones have been identified in diverse tumour types. Whether these are driver or passenger mutations remains uncertain, but the locations of the affected residues indicate that, similarly to the first-identified GBM H3 oncohistones, these mutations may have the potential to substantially override normal patterns of gene expression by interfering with post-translational histone modifications and chromatin remodelling. Further downstream, these changes are associated with alterations in kinase signalling and cellular metabolism, although the underlying mechanisms remain unclear.

These advances in understanding the roles of oncohistones in cancer have revealed new therapeutic targets, and several histone deacetylase inhibitors and tyrosine kinase inhibitors are currently being tested in clinical trials. New precision medicine efforts, which assign therapeutic interventions in clinical trials according to genetic screening of tumours, should improve the chances of success.

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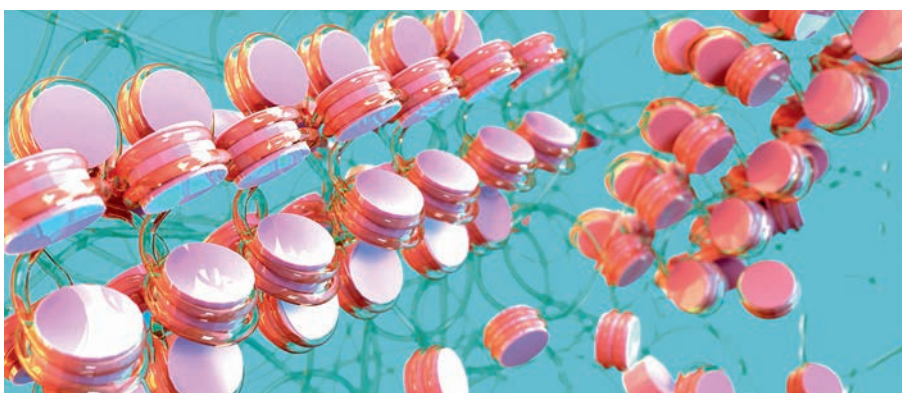

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ORIGINAL ARTICLES Schwartzentruber, J. et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. *Nature* **482**, 226–231 (2012) | Wu, G. et al. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat. Genet.* **44**, 251–253 (2012).

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