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PAPER OF THE MONTH • DECEMBER 2022

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nature genetics

K27M in canonical and noncanonical H3 variants occurs in distinct oligodendroglial cell lineages in brain midline gliomas

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High-grade gliomas driven by mutations in histone 3 variants have unique spatiotemporal distributions, partner alterations and molecular profiles. The contribution of the cell of origin to these differences has been challenging to uncouple from the oncogenic reprogramming induced by the mutation.

This study presents a multimodal profiling of 116 tumors, including single-cell transcriptome and chromatin accessibility, 3D chromatin architecture and histone marks, revealing that the main differences between tumor subtypes are in developmental genes specifying anatomical position. This finding was surprising as many cancers express these genes in a dysregulated manner, and it was expected that tumours, which undergo major changes during the cancer process, would lose the memory of where they originated. Instead, high-grade gliomas faithfully maintained chromatin configuration at developmental genes consistent with anatomically distinct oligodendrocyte precursor cells (OPCs). The pattern of activated genes acted like a “zip code”, allowing the researchers to trace back the cell types and brain regions where each tumour type likely originated. H3.3K27M thalamic gliomas mapped to prosomere 2-derived lineages. In turn, H3.1K27M ACVR1-mutant pontine gliomas uniformly mirrored early ventral NKX6-1+/SHH-dependent brainstem OPCs, whereas H3.3K27M gliomas frequently resemble dorsal PAX3+/BMP-dependent progenitors.

During development, cells in different niches rely on different signaling pathways to grow and differentiate. One subtype of these tumours, H3.1K27M gliomas, which have ACVR1 mutations that activate the bone morphogenetic protein (BMP) pathway, mapped to a cell population that does not normally use BMP during development, suggesting a context-specific vulnerability in H3.1K27M-mutant SHH-dependent ventral OPCs, which rely on acquisition of ACVR1 mutations to drive aberrant BMP signaling required for oncogenesis.

Altogether, this work sheds light on the mechanisms of context dependence of cancer-driving mutations, and links mutational patterns observed in patients to specific anatomical locations in the developing brain and associated vulnerabilities. Identity matters, and it is a critical factor for modeling tumors and for guiding the design of clinical trials.

https://doi.org/10.1038/s41588-022-01205-w