WHITEPAPER

Meet the Marker: H3K27me3

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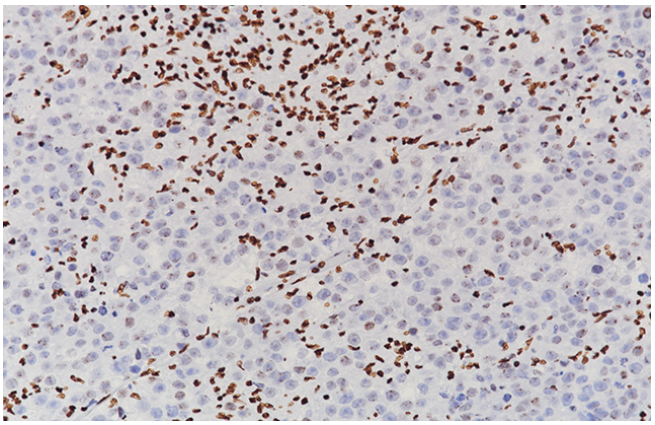
H3K27me3 (trimethylation at lysine 27 of histone H3) is a bivalent epigenetic regulator that silences or represses the gene.[1] H3K27me3 is a downstream target of the Polycomb repressive complex 2 (PRC2) and has diverse roles in embryogenesis and neoplasia as a gene transcription repressor.[2] Immunohistochemical (IHC) evaluation of H3K27me3 expression suggests this biomarker is helpful in neuropathology as it may aid in the diagnosis of tumors such as malignant peripheral nerve sheath tumors (MPNST) and diffuse midline gliomas.

Malignant peripheral nerve sheath tumors are rare neoplasms occurring mostly in adults and representing approximately 4% of all sarcomas.[3] MPNST is often difficult to diagnose due to its divergent morphologic heterogeneity and lack of specific ancillary test.[4] With the emergence of H3K27me3 as an IHC marker, histologic mimics, such as neurofibromas, can be distinguishable from MPNST tumors that show H3K27me3 loss of expression.[4] Research has shown complete loss of H3K27me3 occurs in about 34 - 72% of MPNST (91 - 100% radiation associated, 41 - 71% neurofibromatosis type 1 associated, 32 - 90% sporadic and 0% epithelioid).[2] In MPNSTs, this loss of H3K27me3 expression appears to be associated with higher grade and aggressive behaviors.[2]

H3K27M-mutant diffuse midline gliomas most frequently occur in children and young adults and typically arise in the thalamus, pons, and spinal cord. Research suggests this K27M mutation may lead to altered DNA methylation and gene expression profiles thought to drive gliomagenesis.[5] Solomon *et al.* studied 47 diffuse midline gliomas and, in each case, histone H3-K27M mutant protein staining was diffusely positive throughout all tumor nuclei, suggesting that histone H3 mutation is an early or initiating event in these diffuse midline gliomas. These findings support the ongoing efforts to study the efficacy of therapeutics targeting histone modifying enzymes for these midline gliomas with histone H3 mutations.[5]

Additionally, other neoplasms that may show loss of H3K27me3 expression include meningiomas, radiation associated unclassified sarcomas, radiation associated angiosarcoma, dedifferentiated chondrosarcomas, melanomas, and Merkel cell carcinomas.[2] As in MPNSTs, loss of H3K27me3 may indicate aggressive behavior in meningioma.[6] Conversely, increased expression has been associated with a worse prognosis in some tumors, such as oral squamous cell carcinoma.[7]



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