K27M

Spinal cord glioma grade IV is a rare, diffuse midline glioma. H3 K27M-mutant was classified in the World Health Organization Classification of Tumors of the Central Nervous System 2016 [1].

Pathania et al. report sporadic childhood histone K27M mutant malignant glioma mouse models that faithfully recapitulate the human tumor phenotypes. Beyond emphasizing the importance of correct timing in mouse modeling of cancer, these models will facilitate research to effectively treat this lethal childhood cancer [2].

K27M mutations in both genes substitute a key lysine residue on the histone H3 tail for a methionine, and have been shown to exert biochemical inhibition of the Polycomb Repressor Complex 2 (PRC2) resulting in a global loss of trimethylation of lysine 27 on all histones H3 molecules either wild types or mutated.

Somatic mutations of the H3F3A and HIST1H3B genes encoding the histone H3 variants, H3.3 and H3.1, were identified in high-grade gliomas arising in the thalamus, pons and spinal cord of children and young adults. However, the complete range of patients and locations in which these tumors arise, as well as the morphologic spectrum and associated genetic alterations remain undefined.

They are represented as a separate entity in the WHO classification for tumors of the central nervous system. Interestingly, these tumors display a huge histological variability and diagnoses currently range from low grade astrocytoma (WHO-grade II) to glioblastoma (WHO-grade IV) [3].

Case series

2016

Solomon et al., describe a series of 47 diffuse midline gliomas with histone H3-K27M mutation. The 25 male and 22 female patients ranged in age from 2 to 65 years (median = 14). Tumors were centered not only in the pons, thalamus, and spinal cord, but also in the third ventricle, hypothalamus, pineal region and cerebellum. Patients with pontine gliomas were younger (median = 7 years) than those with thalamic (median = 24 years) or spinal (median = 25 years) tumors. A wide morphologic spectrum was encountered including gliomas with giant cells, epithelioid and rhabdoid cells, primitive neuroectodermal tumor (PNET)-like foci, neuropil-like islands, pilomyxoid features, ependymal-like areas, sarcomatous transformation, ganglionic differentiation and pleomorphic xanthoastrocytoma (PXA)-like areas. In this series, histone H3-K27M mutation was mutually exclusive with IDH1 mutation and EGFR amplification, rarely co-occurred with BRAF-V600E mutation, and was commonly associated with p53 overexpression, ATRX loss (except in pontine gliomas), and monosomy 10 [4].

1)
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H3.3 K27M Mutation on Prognosis and Survival of Grade IV Spinal Cord Glioma on the Basis of New 2016 World Health Organization Classification of the Central Nervous System. Neurosurgery. 2018 May 1. doi: 10.1093/neuros/nyy150. [Epub ahead of print] PubMed PMID: 29718432.
2)

Ramaswamy V, Taylor MD. Pontine Infantile Glioma Simplified. Cancer Cell. 2017 Nov 13;32(5):548-549. doi: 10.1016/j.ccell.2017.10.013. PubMed PMID: 29136501.
3)

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4)

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