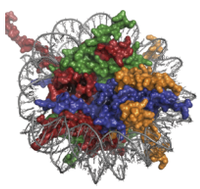
Epigenetics

Major finding: H3K36M-mutant histones prevent mesenchymal progenitor cell differentiation and induce sarcoma.

Mechanism: H3K36M prevents H3K36 methylation, promotes H3K27 methylation, and reduces PRC1 recruitment to genes.

Impact: H3K36M-mediated alterations in histone methylation can disrupt polycomb-mediated gene silencing.

MUTATIONS IN HISTONE H3K36 PREVENT METHYLATION AND DRIVE SARCOMAGENESIS



The majority of chondroblastomas harbor a somatic missense mutation in histone H3 (H3K36M), but the oncogenic mechanisms are not well understood. These and other H3 mutations found in pediatric bone and brain tumors map at or near known sites of histone modifications, including methylation of H3K27 and H3K36, and exhibit a high degree of tumor-type specificity, indicating that the functional consequence of H3 mutations varies based on the tissue of origin. Lu and colleagues investigated the effects of H3K36M mutations in chondroblastoma, which is distinguished by hyperproliferation of immature chondroblast-like cells. Expression of wild-type or mutant (H3K36M) H3 in mouse mesenchymal progenitor cells (MPC) revealed that H3K36M promoted aberrant expression of genes involved in cellular differentiation, reduced the capacity for differentiation into chondrocytes, adipocytes, and osteocytes, and increased expression of transcription factors involved in mesenchymal multipotency. However, H3 mutations found in other tumor types did not affect chondrocytic differentiation, consistent with the tissue specificity of histone mutations in cancer. Further, H3K36M expression in MPCs was sufficient to induce undifferentiated sarcoma formation *in vivo*, and H3K36M and H3K36I mutations were identified in pediatric undifferentiated soft-tissue sarcomas. Impairment of chondrocyte differentiation by H3K36M/I correlated with reduced dimethylation and trimethylation of H3K36 (H3K36me2/3) and increased H3K27me2/3. Like H3K27 mutations in gliomas, which reduce H3K27 methylation by inhibiting the H3K27 methyltransferase polycomb repressive complex 2 (PRC2), H3K36M/I suppressed H3K36 methylation by inhibiting the activity of its cognate methyltransferases SETD2 and NSD2. The corresponding gain of H3K27me2/3 occurred mainly in intergenic regions and recruited PRC1 away from gene-associated regions, resulting in aberrant expression of differentiation genes normally repressed by PRC1. Together, these findings elucidate a role for H3K36 methylation in regulating H3K27 methylation and polycomb complex recruitment, and indicate that specific histone mutations are sufficient to promote sarcomagenesis by impairing MPC differentiation. ■

Lu C, Jain SU, Hoelper D, Bechet D, Molden RC, Ran L, et al. Histone H3K36 mutations promote sarcomagenesis through altered histone methylation landscape. Science 2016;352:844–9.

Sequencing

Major finding: Clinically relevant genomic alterations can be identified in CSF from patients with CNS cancers.

Approach: A panel of cancer-associated genes was sequenced in cell-free DNA from CSF obtained by lumbar puncture.

Impact: Liquid biopsies of the CSF may be useful for monitoring CNS tumor dissemination and evolution.

SEQUENCING DETECTS ONCOGENIC ALTERATIONS IN CEREBROSPINAL FLUID

Tumors affecting the central nervous system (CNS) are challenging to treat, and little is known about the mechanisms of CNS tumor evolution in part because of the difficulty of accessing tumor tissue. Recent studies have indicated that tumor DNA can be detected in the cerebrospinal fluid (CSF) from some patients with CNS cancers, but it is not clear whether detection of clinically relevant genomic alterations by CSF sequencing would be feasible. Pentsova and colleagues performed targeted next-generation sequencing of 341 cancer-associated genes in cell-free DNA (cfDNA) from the CSF of 53 patients and identified clinically relevant somatic alterations that were concordant with the primary tumors in 20 of 32 (63%) of patients with CNS metastases and 6 of 12 (50%) of patients with primary brain tumors, but none in 9 patients without CNS involvement. To determine if drug resistance–associated mutations could be identified in CSF, 12 patients whose CNS tumors progressed during kinase inhibitor treatment were analyzed. Mutations were detected in the CSF of 4 (33%) of these patients that were undetectable prior to treatment, including *EGFR*^{T790M} mutations in two patients and a *KRAS*^{G12A} mutation in one patient with erlotinib-resistant EGFR-mutant non–small cell lung cancer and an acquired *NRAS*^{G12R} mutation in a patient with dabrafenib- and trametinib-resistant melanoma. CSF sequencing also identified mutations in patients with primary brain tumors despite the absence of malignant cells on cytopathological evaluation of the CSF. In one patient, the CSF mutation profile could be compared to that of the original tumor and a recurrent tumor sample obtained 3 weeks after CSF collection. All three samples shared several common mutations, whereas the CSF and recurrent tumor samples harbored distinct mutations. Collectively, these findings demonstrate the feasibility of next-generation sequencing of CSF and indicate that liquid biopsies of the CSF may potentially be used to monitor CNS tumor progression. ■

Pentsova EI, Shah RH, Tang J, Boire A, You D, Briggs S, et al. Evaluating cancer of the central nervous system through next-generation sequencing of cerebrospinal fluid. J Clin Oncol 2016 May 9 [Epub ahead of print].

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