Epigenetic Profiling Reveals a Unique Histone Code in Chordoma

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Introduction

Pathognomonic genetic "driver" lesions to explain the brachyury transcriptional program have not been described in chordoma. Herein we characterize the epigenetic histone, methyl-genomic and somatic chromatin-modifying genotypic (CMG) landscape of chordoma.

Methods

Six chordomas with matched germline tissue representing a spectrum of location (sacral, clival, mobile spine), histopathology (classical and dedifferentiated) and stage (primary and post-irradiation recurrences) underwent mass spectrometric histone profiling. Genotype was obtained via exome sequencing, and enhanced-representation reduced bisulfite sequencing yielded genomic methylation data.

Learning Objectives

By the conclusion of this session, participants should be able to 1) discuss the pathophysiology of chordoma, 2) discuss, in small groups, the known driver molecular lesions in the disease, and 3) identify current treatment strategies for the disease.

Results

Histone marks were highly conserved across chordoma samples regardless of site of origin or histopathology. Pathognomonic histone marks included hypermethylated lysine 27 on H3.1 (H3.1K27) compared to a cohort of 6 cancer cell lines ($p = 4.8e\text{-}10$), marks associated with transcriptional repression. Other significant alterations included H3K4 hypermethylation, predicted on the basis of brachyury overexpression. Genotype further predicted some degree of variability across chordoma samples, with CMG alterations including lysine demethylase loss associated with hypermethylation at the predicted residues.

Conclusions

In this first utilization of mass spectrometric analysis of a solid tumor, chordoma harbors a histone code distinct from other profiled neoplastic and normal tissues.

References available upon request