Hox gene

Hox genes, a subset of homeotic genes, are a group of related genes that control the body plan of an embryo along the head-tail axis. After the embryonic segments have formed, the Hox proteins determine the type of appendages (e.g. legs, antennae, and wings in fruit flies) or the different types of vertebrae (in humans) that will form on a segment. Hox proteins thus confer segmental identity, but do not form the actual segments themselves.

An analogy for the Hox genes can be made to the role of a play director that calls which scene the actors should carry out next. If the play director calls the scenes in the wrong order, the overall play will be presented in the wrong order. Similarly, mutations in the Hox genes can result in body parts and limbs in the wrong place along the body. Like a play director, the Hox genes do not act in the play or participate in limb formation themselves.

The protein product of each Hox gene is a transcription factor. Each Hox gene contains a well-conserved DNA sequence known as the homeobox, of which the term “Hox” is a contraction. Hox genes are thus a subset of the homeobox transcription factor genes. In many animals, the organization of the Hox genes in the chromosome is the same as the order of their expression along the anterior-posterior axis of the developing animal, and are thus said to display colinearity.

DNA methylation patterns delineate clinically relevant subgroups for meningioma classification. Paramasivam et al., previously established the six meningioma methylation classes (MC) benign 1-3, intermediate A and B, and malignant.

They set out to identify subgroup-specific mutational patterns and gene regulation. Whole genome sequencing was performed on 62 samples across all MCs and WHO grades from 62 patients with matched blood control, including 40 sporadic meningiomas and 22 meningiomas arising after radiation (Mrad). RNA sequencing was added for 18 of these cases and chromatin-immunoprecipitation for histone H3 lysine 27 acetylation (H3K27ac) followed by sequencing (ChIP-seq) for 16 samples. Besides the known mutations in meningioma, structural variants were found as the mechanism of NF2 inactivation in a small subset (5%) of sporadic meningiomas, similar to previous reports for Mrad. Aberrations of DMD were found to be enriched in MCs with NF2 mutations, and DMD was among the most differentially upregulated genes in NF2 mutant compared to NF2 wild-type cases. The mutational signature AC3, which has been associated with defects in homologous recombination repair (HRR), was detected in both sporadic meningioma and Mrad, but widely distributed across the genome in sporadic cases and enriched near genomic breakpoints in Mrad. Compared to the other MCs, the number of single nucleotide variants matching the AC3 pattern was significantly higher in the malignant MC, which also exhibited higher genomic instability, determined by the numbers of both large segments affected by copy number alterations and breakpoints between large segments. ChIP-seq analysis for H3K27ac revealed a specific activation of genes regulated by the transcription factor FOXM1 in the malignant MC. This analysis also revealed a super enhancer near the HOXD gene cluster in this MC, which, together with general upregulation of HOX genes in the malignant MC, indicates a role of HOX genes in meningioma aggressiveness. This data elucidates the biological mechanisms rendering different epigenetic subgroups of meningiomas, and suggests leveraging homologous recombination repair (HRR) as a novel therapeutic target [1)].

HOX gene dysregulation

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[1)]

Paramasivam N, Hübschmann D, Toprak UH, Ishaque N, Neidert M, Schrimpf D, Stichel D, Reuss D, Sievers P, Reinhardt A, Wefers AK, Jones DTW, Gu Z, Werner J, Uhrig S, Wirsching HG, Schick M, Bewerunge-Hudler M, Beck K, Brehmer S, Urbschat S, Seiz-Rosenhagen M, Hänggi D, Herold-Mende C, Ketter R, Eils R, Ram Z, Pfister SM, Wick W, Weller M, Grossmann R, von Deimling A, Schlesner M, Sahm F. Mutational patterns and regulatory networks in epigenetic subgroups of meningioma. Acta Neuropathol. 2019 May 8. doi: 10.1007/s00401-019-02008-w. [Epub ahead of print] PubMed PMID: 31069492.