Reduced HOXB13 expression in neuroendocrine prostate cancer represents a loss of prostate identity

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Background: About 30% patients acquire the neuroendocrine (NE) phenotype after androgen deprivation therapy fails. Evidences support that neuroendocrine prostate cancer (NEPCa) arise from prostate adenocarcinoma (AdPCa) through trans-differentiation. HOXB13, a homeobox gene, is primarily expressed in prostate. Previous research suggests that the different HOX genes expression pattern represents the anatomic origins of cells.

Methods: Using publicly available RNASeq data, we analyzed the expression of HOX genes in 1019 human cancer cell lines that reflect 24 anatomic origins. Additionally, immunohistochemistry (IHC), Western blot and RT-qPCR were used to assess the expression of HOXB13. Dual immunofluorescence staining was used to visualize the expression of HOXB13 in prostate glands. In silico analysis based on R was used to perform data mining.

Results: We established HOX codes for 24 anatomic origins using the transcriptomic data of 1019 human cancer cell lines. We found that NEPCa cell line H660 has a distinct expression pattern of HOX genes, different from prostatic HOX code. Additionally, analysis of RNASeq data of human NEPCa samples indicated that AdPCa tumors maintained prostatic HOX code but majority NEPCa tumors lost prostate HOX code. However, the NEPCa samples did not show consistent correlation with the HOX codes of any tissues. This suggests that NEPCa tumors have lost prostate identity but have yet gained a clear-cut new tissue identity. Further, we found that HOXB13 was expressed in prostatic luminal epithelial cells. The expression of HOXB13 was elevated along with AdPCa progression but was decreased in NEPCa. Furthermore, we found the all-trans retinoic acid induced the expression of HOXB13, AR and AR targeting genes in NEPCa cells.

Conclusion: 1) HOXB13 expression is reduced or lost in NEPCa. 2) A loss of prostate-specific HOX code in NEPCa represents a loss of prostatic identity. 3) the lost expression of HOXB13 in NEPCa is reversible. **Significance:** 1) The HOX codes we established can be used in pan cancer research to identify the tissue of origin and to study the trans-differentiation of cancer cells. 2) We propose all-trans retinoic acid can be used to revert NE differentiation in human patients.

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