HoxB-13 in Prostate and Colorectal Cancer Development

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Hox homeobox genes are known to function as a set of transcription factors, merely due to the presence of DNA-binding homeodomain. *Hox* genes function during development to regulate axial regional specification during embryonic development. Therefore, *Hox* genes are expressed in a tissue-specific and frequently stage-related fashion. The *hox-13* paralog is especially important to the development of the caudal extent of the body axis, including the prostate and colon. Hoxb13 has been recently found to limit proliferation and activate programmed cell death in secondary neural tube and caudal mesoderm. In mesoderm-derived prostate gland, Hoxb13 is highly expressed from the embryonic stage to adulthood and Hoxb13 knockout mice retain swollen prostate gland. However, precise role of Hoxb13 in this organ and molecular mechanisms how Hoxb13 functions are entirely unknown.

In prostate, expression pattern of HOXB13 seems to correlate with androgen-receptor (AR), suggesting that HOXB13 may be involved in AR signaling to modulate the growth of normal and cancerous prostate cells. In fact, HOXB13 interacts with AR to suppress androgen-mediated AR signaling and subsequently inhibits the growth of AR-positive LNCaP cells. HOXB13-mediated growth suppression can be counteracted by the overexpression of hormone-activated AR. In AR-negative PC3 cells, however, HOXB13's growth suppressive function is accomplished through the transcriptional inhibition of T cell factor-4 (TCF-4). Accordingly, HOXB13 suppressed TCF-4 mediated transactivation and the expression of its responsive gene, *c-myc*. Therefore, HOXB13 seems to regulate AR, TCF-4, or both signaling pathways, depending on the status of AR. In other words, HOXB13 and AR may need to coexist and may functionally counteract each other in regulating the growth and progression of prostate cancer cells. Although no difference is found in HOXB13 expression between tumors and matching normal tissues, over 70% of colorectal tumors lost the expression of HOXB13. Considering that mutations in APC/ß-catenin signaling cascade is a decisive event for colorectal tumorigenesis and involved in over 90 % of colorectal cancers, loss of HOXB13 may be an another step for colorectal cell to acquire growth advantage during the transformation process.

Our ultimate goal is to understand the mechanistic and functional connection between HOXB13 and AR and/or TCF-4 signaling pathways. Achieving this goal will further explain how HOXB13 can play a role as a mediator to regulate these two important growth signals.