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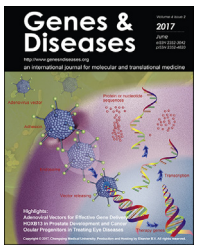

REVIEW ARTICLE

HOXB13 mutations and binding partners in prostate development and cancer: Function, clinical significance, and future directions

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Abstract The recent and exciting discovery of germline *HOXB13* mutations in familial prostate cancer has brought HOX signaling to the forefront of prostate cancer research. An enhanced understanding of HOX signaling, and the co-factors regulating HOX protein specificity and transcriptional regulation, has the high potential to elucidate novel approaches to prevent, diagnose, stage, and treat prostate cancer. Toward our understanding of HOX biology in prostate development and prostate cancer, basic research in developmental model systems as well as other tumor sites provides a mechanistic framework to inform future studies in prostate biology. Here we describe our current understanding of HOX signaling in genitourinary development and cancer, current clinical data of *HOXB13* mutations in multiple cancers including prostate cancer, and the role of HOX protein co-factors in development and cancer. These data highlight numerous gaps in our understanding of HOX function in the prostate, and present numerous potentially impactful mechanistic and clinical opportunities for future investigation.

Abbreviations: ADT, Androgen Deprivation Therapy; AR, Androgen Receptor; HOX, Homeobox; MEIS, Murine Ectopic Integration Site; PIN, Prostatic Intraepithelial Neoplasia; PSA, Prostate-Specific Antigen; TALE, Three Amino Acid Loop Extension.

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Introduction

Prostate cancer is the most common non-cutaneous cancer and the second leading cause of cancer related mortalities among American men.[1] The recent and exciting identification of germline *HOXB13 (G84E)* mutations within a subset of familial prostate cancers by Isaacs and Cooney in 2012 highlights a novel set of genes and transcriptional signaling pathways to understand prostate tumor etiology and develop new treatment modalities to combat prostate tumor initiation and progression.[2] Prior to this discovery, much was already known regarding the expression and function of *HOX* genes, and their co-factors, in development and cancer. However, there remain significant gaps in our current understanding of HOX biology in prostate development and disease.

The role of *HOX* genes in organismal development

HOX proteins are highly evolutionarily conserved, homeodomain-containing transcription factors best known for their roles in body axis patterning and tissue differentiation of developing embryos.[3,4] Furthermore, recent studies have shown HOX proteins not only have a role development and organogenesis, but they also contribute to the control of several other processes into adulthood such as cell proliferation, cell cycle, apoptosis, cell differentiation, and cell migration.[3,5,6] In humans, the 39 HOX proteins are divided into four *HOX* gene clusters: A, B, C, and D located on chromosomes 7p15, 17q21.2, 12q13, and 2q31 respectively.[7] Each cluster is comprised of paralogous genes 1—13 whose 3′ to 5′ organization and expression both follow a pattern of spatial and temporal co-linearity with development, although not every paralog is present in each cluster. The 3′ *HOX* genes are most highly expressed in the anterior body regions that arise early in development, while the 5′ *HOX* genes encode more posterior regions that form later in development. The term, "HOX Code," refers to the phenomenon where tissue specificity is determined by nested and partially overlapping expression of several *HOX* genes in a given region. The most 5′ *HOX* gene expressed in a given tissue, however, has dominance in determining a specific tissues' identity compared to the more 3′ *HOX* gene that may be co-expressed.[8] For example, while 36 of the 39 *HOX* genes are expressed at a detectable level by qRT-PCR in a gross sample of human prostate tissue, it is the 5′ *HOX* genes like *HOXA13* and *HOXB13* that are most highly expressed and most significantly confer prostatic identity.[9] Several excellent and in-depth reviews have already been published on the general role of *HOX* genes in development and cancer.[3,6,10—12]

HOX expression in male reproductive system

The male reproductive tract is derived from two main developmental structures: the Wolffian (mesonephric) duct, which gives rise to the testis, epididymis, vas deferens, and seminal vesicle; and the urogenital sinus (UGS), which gives rise to the prostate, bulbourethral (Cowper's) glad, bladder, and urethra.[13] Given that the reproductive tract is one of the most posterior systems in the body, expression of primarily posterior *HOX* genes like those in paralog groups 9—13 is most commonly observed (Fig. 1A and B).[4,8,14] However, several 3′ *HOX* genes are also expressed in the testis and are thought to have critical roles in spermatogenesis rather than in testis function (Fig. 1A).[14]

Many of the *Hox* paralogs have redundant and overlapping functions rendering the identification of specific roles for each gene complicated; however, some insight has been gained by observing phenotypes of various *Hox* gene knockout rodents. For example, while homozygous loss of *Hoxa13* (*Hoxa13*$^{-/-}$) is considered embryonic lethal due to the perceived role of *Hoxa13* in umbilical artery maintenance, examination of *Hoxa13*$^{-/-}$ fetuses shows severe hypoplasia of the urogenital sinus and arrested or delayed rostral-to-caudal progression of Müllerian ducts.[15] Additionally, *Hoxd13* deficient mice (*Hoxd13*$^{-/-}$) reveal diminished folding in the seminal vesicle stromal sheath, reduced ductal branching and size of the dorsal and ventral prostate lobes, and agenesis of the bulbourethral gland.[16] Furthermore, compound homozygous mutants (double *Hoxa13*$^{-/-}$ and *Hoxd13*$^{-/-}$) fetuses have undetectable development of the genital tubercle, nor any distinct hindgut and urogenital sinus, among other deformities.[15] In contrast, mice expressing *Hoxb13* with a loss-of-function mutation in the homeodomain show no gross morphological defects, but rather have prostate ventral lobe-specific defects in histology and secretory function.[17] Histologically, ventral lobe epithelium from *Hoxb13* mutant mice are composed of simple cuboidal rather than the tall columnar luminal cells that make up healthy prostate epithelium, and are also devoid of the ventral-specific secretory proteins p12 and p25.[17] For a thorough review of reproductive system phenotypes observed with various 5′ *Hox* gene knockouts, please refer to "Homeobox genes and the male reproductive system" by Rao and Wilkinson.[18]

In addition to the spatial and temporal patterns of *Hox* gene expression there is also clear species specificity to the pattern. This is especially well demonstrated when noting the *Hox* patterns of the prostate in developing mice, rats, and adult humans; however, it should be noted that there is very little data regarding *HOX* expression in the developing embryonic human prostate. While at a glance, many of the same *HOX* genes are expressed in all three of these species, the timing, location, and amount of expression can all vary. In murine prostates, Bushman et al found that *Hoxa10* expression peaked at embryonic day 19 (E19) and decreased rapidly after birth to near undetectable levels by post-natal day 5 (P5).[19] They also showed that *Hoxa13* and *Hoxd13* expression both peaked around E15 and steadily diminished from there into adulthood; spatially, both *Hoxa13* and *Hoxd13* had epididymal expression which peaked in the seminal vesicle.[20] This observation of *Hoxa13* and *Hoxd13* expression appears to contrast to the work of Prins et al within the rat prostate demonstrating a postnatal increase in expression that is maintained into adulthood for all three of the previously mentioned genes.[4] They also demonstrated that *Hoxa13* and *Hoxd13* peaked in expression within the dorsal prostate rather than seminal vesicle, and also had a clear anterior boundary at the epididymis.[4] Furthermore, in the rat prostate, Prins et al demonstrated