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THE ROLE OF HOXB13 IN BIOLOGICAL MEDICINE - A GENERAL OVERVIEW

Biochemistry

Mr. Sagar M Nitturkar* PhD Research Scholar *Corresponding Author
Dr. Anuradha B Patil Professor
Dr. Rajendra B Nerli Professor & Head Department of Urology

ABSTRACT

In the development of epithelial prostate gland, the homeobox protein (HOXB13) plays a crucial role. The prostate gland pathogenesis is thought to be aided by the overexpression of HOXB13, which is observed throughout the development of prostatic tissue's malignant transformation. The tumor suppressor protein p21 is hypothesized to be inhibited by HOXB13 in androgen-deficient circumstances. To have a deeper knowledge of HOXB13's function in prostate cancer, its crucial cascade partners in the ventral prostate development must be clarified. In this review, we discuss the different roles of HOXB13 in other malignancies along with the prostate cancer including its functions such as wound healing, cellular differentiation, and angiogenesis.

KEYWORDS

homeobox protein, prostate, tumor suppressor protein, prostate cancer, malignancies, angiogenesis

INTRODUCTION

The homeobox or Hox genes are a class of regulatory genes that primarily operate as transcription factors and encode for nuclear proteins known as homeoproteins. They can bind DNA sequences specifically thanks to the homeodomain, a protein domain encoded by the homeobox (HD) genes. During embryogenesis, the homeobox genes serve as master switches for the formation of numerous body structures. They play a significant role in the control of anterior/posterior patterning of the prostate gland and are recognized as highly conserved genes [1]. The second biggest class of homeodomain-containing proteins are those encoded by the Hox genes transcription factors based on sequence [2].

A 60 amino acid long homeodomain that binds to DNA is encoded by a highly conserved sequence. In all animals, including humans, hox gene clusters regulate the polarity of the embryo and body segmentation throughout embryogenesis. These genes exhibit coordinated expression in the limb and genital tubercle [3,4]. Hox (A, B, C, D) clusters are distributed on chromosomes 7, 17, 12, and 2 in succession. There are four sets of hox genes clustered in unlinked complexes across the human genome.

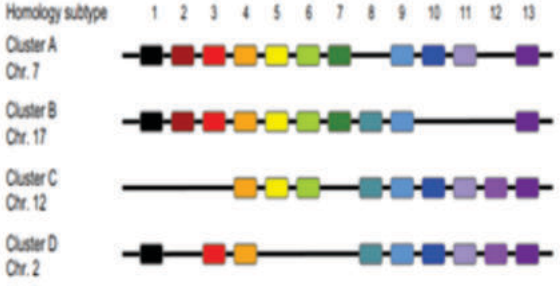

Figure 1: Genomic Architecture of HOX Genes
(Source: Dysregulation of the homeobox transcription factor gene HOXB13: role in prostate cancer: Brennan Decker. Elaine A Ostrander)

The hox genes of the four clusters are organized into 13 paralog groups, and their expression along the anterior-posterior (AP) axis (from anterior to posterior) is determined by their (3'-5') position in the genome [2]. Hox genes are also expressed in differentiated organs both during and after the organogenesis phase [1]. Any mutation can result in harmful abnormalities because these genes are crucial for the development of body parts. Alterations in the Hox gene's activity have recently been linked to numerous types of cancer, according to several studies [4-9]. The HOX B cluster's final recognized paralog member is the HOXB13 gene. Despite being about 70 kb apart from HOX B9, it is transcribed in the same direction as the other HOX B genes [10]. HOXB13 displays spatial and temporal co-linearity within the main body axis while being physically apart from the cluster. It is mostly expressed in the urogenital sinus, digestive system, and tail-bud and posterior domains of the spinal cord [10,11]. the gene HOXB13 plays a crucial part in the development of the prostate and its secretory processes [12,13]. Additionally, it regulates androgen receptors (AR) in a polyvalent manner by either activating or suppressing the transcription of several AR target genes [14].

There are conflicting findings on HOXB13's precise function in prostate cancer (PCa). HOXB13 has a dual and contradictory function that, in certain circumstances, inhibits PCa cell growth and, in others, encourages malignancy. Our study aimed to discuss the different roles of HOXB13 in other malignancies along with the prostate cancer including its functions such as wound healing, cellular differentiation, and angiogenesis. present additional evidence of HOXB13's significance in PCa and the reliability of its use in diagnosis and prediction of the PCa at the early stages.

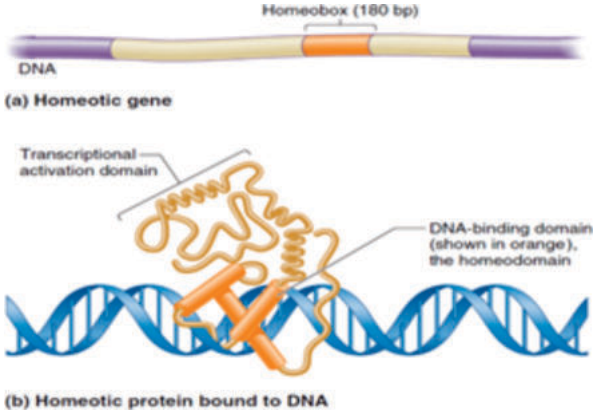

Figure 2: A Homeotic Gene, Shown In Tan And Orange, Contains A 180-bp Homeobox, Which Codes For A DNA-Binding Protein Region Called The Homeodomain. This Binds At An Enhancer Genetic Regulatory Element And Activates Transcription.
(Source: Brooker RJ: Genetics: Analysis & Principles, 3rd ed. New York: McGraw-Hill, 2008.)

HOXB13-Structural Description

The Abdominal-B (Abd-B) homeobox family contains the HOXB13 gene, which codes for a transcription factor. HOXB13 is one of a group of hox genes that are in the 17q21–17q22 region of chromosome 17. 3467 bp is the estimated length of the transcript, which codes for a

protein of 284 amino acids. The DNA binding domain, also known as the homeodomain (DBD), which is composed of 60 amino acid residues and is highly conserved across species, is what gives HOX proteins their distinctive properties. To evaluate the tissue specific activity for various hox proteins, the ultrastructure study of DBD revealed the existence of three alpha helices, a highly conserved DNA binding domain, and a distinctive sequence outside the homeodomain [15].

Biological Actions Of HOXB13 Gene

All hox proteins, overall, function as transcription factors that control the genes involved in body segmentation during embryogenesis [1]. Hox genes regulate the axial determination of the anterior and posterior. Hox gene dysfunction can result in severe bodily deformities. Hox genes also contribute to the growth of secondary sex traits including the mammary glands [16, 17] and male accessory sexual organs in a variety of ways [3,18-20].

A) Prostate Gland Epithelial Differentiation And The Function Of HOXB13

The HOX 13 paralogs play a crucial role in the formation of the prostate. Reduced branching has been seen in mouse prostate ducts carrying mutant HOXA13 and HOXD13 [18-21]. The normal development of the prostate also depends on the non-Hox homeodomain protein Nkx3.1, whose expression is androgen-dependent [22,23]. The caudal extension of the spinal cord, the tail bud, and the urogenital sinus have all been linked to HOXB13 expression [10,11]. HoxB13 is highly expressed in the prostate gland originating from the urogenital sinus and is not controlled by androgen stimulation, according to research [11,13]. According to reports, HOXB13 expression is confined to the prostate in adult mice, particularly the ventral lobe, descending colon, and rectum, which are all derived from the posterior endoderm [11]. Contrary to other prostate-specific genes, the higher accumulation of HOXB13 mRNA in castrated mice is evidence that HOXB13 expresses androgen-independently [11,24]. Mice with mutant HOXB13 alleles had 100% penetrance, an atypical shape of the luminal epithelial cells, and a complete absence of the secretory proteins p12 and p25 in the ventral prostate [12]. HOXB13 is essential for differentiation processes like lipogenesis as well as the regulation of maintaining a balance between cell growth and proliferation [14]. HOXB13 co-regulates the nuclear receptor family protein AR. The proliferation and differentiation of cells in a healthy prostate gland are controlled by androgen stimulation via AR. For growth-specific genes including c-myc, fos, and jun to begin expressing, the AR works with several coactivators and HOXB13.

B) HOXB13's Contribution In Skin's Reaction To Wound Healing

Studies have revealed that the protein during foetal skin development is localized in the cytoplasm in addition to being expressed in the posterior endoderm. HOXB13 expression is downregulated in foetal skin that heals without scars, but it is unaffected in adult wounds, according to studies in SCID mice transplanted with human foetal and adult skin [25]. However, the hyperproliferative epidermis linked to Kaposi's sarcoma is where nuclear HOXB13 is more seldom expressed. The involvement of HOXB13 in the formation of adult skin was shown by its overexpression in the keratinocytes of the human foreskin [26] and the epidermal keratinocytes of the rat [27]. The excessively cornified rat keratinocytes caused by HOXB13 overexpression highlight a potential role in the pathophysiology of skin [28]. The function of HOXB13 molecular partners is evident and the associated signaling cascade is in its early stages.

C) HOXB13's Significance In Angiogenesis And Endothelial Differentiation

Four HOX genes—HOXA7, HOXB3, HOXA3, and HOXB13—have recently been linked to major alterations in the expression patterns during angiogenesis in human bone marrow-derived mesenchymal stem cells (hMSCs). During endothelial cell development, HOXA3 and HOXB13 expression levels fell whereas those of HOXA7 and HOXB3 were drastically enhanced. Evidence Certain studies support the hypothesis that these Hox genes, especially HOXB13, are crucial for hMSC's angiogenesis [28].

D) The Function of HOXB13 in Prostate Cancer

PCa accounts for 15% of cancer diagnoses in males and is the fourth most prevalent malignancy in the globe [29,30]. PCa is the second-leading cause of death among American men in the country [31]. About 6 per 100,000 people in the Middle East have PCa, while the fatality rate is 5 per 100,000 [32]. Similarly, Prostate cancer incidence, clinical features, and fatality are very variable within India, with an urban population having a higher incidence. In several regions of India, the disease's prevalence is rising. There are only a few population-based cancer registries in India who reported the incidence data on PCa, further information on the actual incidence of the disease is scarce [33]. The androgen ligand encourages prostate tumor cell survival and growth after interacting with its receptor [34]. Androgen ablation or refraction with androgen antagonists is the main treatment that lowers prostate cancer risk. Prostate cancer cells that have undergone androgen ablation experience cell cycle arrest [35,36], however a return of androgen independent tumor is the main disadvantage of this therapy. It has been conclusively demonstrated that prostate cancer still develops in cells devoid of androgen [33,34,37]. Due to the multifocal nature of the malignancy, the causes of the prostate tumor growth despite androgen ablation are not fully understood.

A versatile AR regulator, HOXB13 controls the transcriptional activation or repression of several AR target genes. The dual role of HOXB13 in both positively and negatively regulating the interaction of AR with chromatin accounts for most of its intricate effect on AR transcriptional activity. As a result, HOXB13 plays a crucial function in the control of the cellular response to androgens [14]. As previously mentioned, HOXB13 inhibits androgen-mediated signaling, which in turn decreases the development of prostate cells. Additionally, HOXB13 controls prostate cancer cell proliferation by negatively regulating the expression of T-Cell Factor 4 (TCF-4), which in turn down-regulates or inhibits the TCF-4 responsive genes c-myc and cyclin D1 [38].

However, HOXB13 overexpression in LNCaP prostate cancer cells and androgen-independent cancer cell development advancement that was triggered by overexpressed HOXB13 were found in a recent analysis. The tumor suppressor gene p21 appears to be inhibited by HOXB13, which then appears to up-regulate E2F transcription factor. This results in the release of cyclin-dependent kinase 2, which then phosphorylates RB protein, releasing E2F1 and activating factors for cell proliferation like c-myc and p107 proteins. When there is an androgen deficiency, E2F stimulates prostate cancer cells to proliferate [9]. These results demonstrate that whereas HOXB13 inhibits the proliferation of prostate cancer cells in the PC3 cell line by controlling androgen-mediated signals, higher levels of HOXB13 expression are linked to the advancement of tumor growth in the LNCaP cell line, which is androgen deficient. Recent research has linked the recurrent germ line mutation G84E of HOXB13 to an increased risk of PCa in men of European heritage [39].

E) HOXB13's Relevance In Other Malignancies

In addition to these malignancies, HOXB13 is also involved in malignant melanomas, endometrial, breast, ovarian, and renal tumors. HOXB13 seems to function as a tumor suppressor in malignant melanoma and kidney tumors. It has been demonstrated that methylation inactivates HOXB13 in renal carcinoma cells, and when exogenous HOXB13 is added, tumor invasion is prevented [7]. Likewise, re-expression of HOXB13 in malignant melanoma cells prevented the development of tumors [40]. On the other side, HOXB13 acts as a growth promoter in hormone responsive cancers such ovarian, breast, and endometrial [5,6,8]. The invasiveness of ovarian, breast, and endometrial cancer cells is linked to HOXB13 overexpression. HOXB13 overexpression in breast cancer cells renders the cells resistant to tamoxifen treatment [41]. As a result, it has already been demonstrated that HOXB13 is relevant in predicting the pathologic status of breast cancer.

CONCLUSION

The correct growth of the prostate gland depends on HOXB13 gene. Its expression in the gland is unaffected by androgen stimulation and is necessary for the proper secretory function of the prostate as well as for the regular morphology of the prostatic epithelium. According to the research so far, HOX genes play numerous roles in embryonic and differentiated tissue development. The large size of the HOX gene family, tightly regulated spatial and temporal expression patterns, and slight variations in homeodomain sequences that result in specificity for different enhancer DNA sequences explain much of this functional diversity. The number of HOX genes, as well as the number of HOX gene clusters, varies greatly across phyla. Paralogous HOX gene

homology subtypes defined by homeobox sequence similarity have resulted from genomic amplification and evolutionary divergence. Furthermore, larger genomic events resulted in the amplification of entire HOX gene clusters, whereas subsequent losses resulted in clusters containing only a subset of the homolog subtypes. The increased number of genes and clusters enables HOX genes to play a wide range of roles. Despite this variation, the basic mechanism of HOX-mediated anterior-posterior patterning is highly conserved across species, manifesting in vertebrates as typical clustered genomic architecture and collinear pattern of expression, but most importantly as extensive coding sequence homology, particularly of the characteristic homeobox domain. HOXB13 likely plays a significant role in prostate cancer. It also functions as a tumor suppressor, which prevents cells from growing and dividing too quickly or in an uncontrolled manner and thus further research is required to establish conclusive evidence supporting the overexpression of HOXB13 in androgen-deficient prostate cancer cells as a biomarker for the prognosis of PCa.

REFERENCES

1. Krumlauf, R. (1994). Hox genes in vertebrate development. Cell, 78(2), 191-201.
2. Hueber, S. D., & Lohmann, I. (2008). Shaping segments: Hox gene function in the genomic age. Bioessays, 30(10), 965-979.
3. Dolte, P., Izpisua-Belmonte, J. C., Brown, J. M., Tickle, C., & Duboule, D. (1991). Hox-4 genes and the morphogenesis of vertebrate genitalia. Genes Dev, 5, 1767-1776.
4. Yokouchi, Y., Sasaki, H., & Kuroiwa, A. (1991). Homeobox gene expression correlated with the bifurcation process of limb cartilage development. Nature, 353(6343), 443-445.
5. Miao, J., Wang, Z., Provencher, H., Muir, B., Dahiya, S., Carney, E., ... & Orsulic, S. (2007). HOXB13 promotes ovarian cancer progression. Proceedings of the National Academy of Sciences, 104(43), 17093-17098.
6. Vaksman, O., Tropé, C., Davidson, B., & Reich, R. (2014). Exosome-derived miRNAs and ovarian carcinoma progression. Carcinogenesis, 35(9), 2113-2120.
7. Okuda, H., Toyota, M., Ishida, W., Furihata, M., Tsuchiya, M., Kamada, M., ... & Shuin, T. (2006). Epigenetic inactivation of the candidate tumor suppressor gene HOXB13 in human renal cell carcinoma. Oncogene, 25(12), 1733-1742.
8. Zhao, Y., Yamashita, T., & Ishikawa, M. (2005). Regulation of tumor invasion by HOXB13 gene overexpressed in human endometrial cancer. Oncology reports, 13(4), 721-726.
10. Zeltser, L., Desplan, C., & Heintz, N. (1996). Hoxb-13: a new Hox gene in a distant region of the HOXB cluster maintains colinearity. Development, 122(8), 2475-2484.
11. Sreenath, T., Orosz, A., Fujita, K., & Bieberich, C. J. (1999). Androgen□independent expression of hoxb□13 in the mouse prostate. The Prostate, 41(3), 203-207.
12. Economides, K. D., & Capecchi, M. R. (2003). Hoxb13 is required for normal differentiation and secretory function of the ventral prostate.
13. Huang, L., Pu, Y., Hepps, D., Danielpour, D., & Prins, G. S. (2007). Posterior Hox gene expression and differential androgen regulation in the developing and adult rat prostate lobes. Endocrinology, 148(3), 1235-1245.
14. Norris, J. D., Chang, C. Y., Wittmann, B. M., Kunder, R. S., Cui, H., Fan, D., ... & McDonnell, D. P. (2009). The homeodomain protein HOXB13 regulates the cellular response to androgens. Molecular cell, 36(3), 405-416.
15. Chauvet, S., Merabet, S., Bilder, D., Scott, M. P., Pradel, J., & Graba, Y. (2000). Distinct hox protein sequences determine specificity in different tissues. Proceedings of the National Academy of Sciences, 97(8), 4064-4069.
16. Stupar, R. M. (2010). Into the wild: The soybean genome meets its undomesticated relative. Proceedings of the National Academy of Sciences, 107(51), 21947-21948.
17. Garcia□Gasca, A., & Spyropoulos, D. D. (2000). Differential mammary morphogenesis along the anteroposterior axis in Hoxc6 gene targeted mice. Developmental dynamics: an official publication of the American Association of Anatomists, 219(2), 261-276.
18. PODLASEK, C. A., CLEMENS, J. Q., & BUSHMAN, W. (1999). Hoxa-13 gene mutation results in abnormal seminal vesicle and prostate development. The Journal of urology, 161(5), 1655-1661.
19. Podlasek, C. A., Duboule, D., & Bushman, W. (1997). Male accessory sex organ morphogenesis is altered by loss of function of Hoxd□13. Developmental dynamics: an official publication of the American Association of Anatomists, 208(4), 454-465.13. Developmental Dynamics, 208(4), 454-465 (1997) DOI: 10.1002/(SICI)1097-0177(199704)208: 4<454:AID-AJA2>3.0.CO;2-H
20. Podlasek, C. A., Seo, R. M., Clemens, J. Q., Ma, L., Maas, R. L., & Bushman, W. (1999). Hoxa□10 deficient male mice exhibit abnormal development of the accessory sex organs. Developmental dynamics: an official publication of the American Association of Anatomists, 214(1), 1-12.
21. Warot, X., Fromental-Ramain, C., Fraulob, V., Chambon, P., & Dollé, P. (1997). Gene dosage-dependent effects of the Hoxa-13 and Hoxd-13 mutations on morphogenesis of the terminal parts of the digestive and urogenital tracts. Development, 124(23), 4781-4791.
22. Bieberich, C. J., Fujita, K., He, W. W., & Jay, G. (1996). Prostate-specific and androgen-dependent expression of a novel homeobox gene. Journal of Biological Chemistry, 271(50), 31779-31782.
23. Sciavolino, P. J., Abrams, E. W., Yang, L., Austenberg, L. P., Shen, M. M., & Abate□Shen, C. (1997). Tissue□specific expression of murine Nkx3. 1 in the male urogenital system. Developmental dynamics: an official publication of the American Association of Anatomists, 209(1), 127-138.
24. McMullin, R. P., Dobi, A., Mutton, L. N., Orosz, A., Maheshwari, S., Shashikant, C. S., & Bieberich, C. J. (2010). A FOXA1-binding enhancer regulates Hoxb13 expression in the prostate gland. Proceedings of the National Academy of Sciences, 107(1), 98-103.
25. Stelnicki EJ, Arbeit J, Cass DL, Saner C, Harrison M and L. C.: Modulation of the human homeobox genes PRX-2 and HOXB13 in scarless fetal wounds. J Invest Dermatol, 111(1), 7 (1998).
26. Kömüves, L. G., Ma, X. K., Stelnicki, E., Rozenfeld, S., Oda, Y., & Largman, C. (2003). HOXB13 homeodomain protein is cytoplasmic throughout fetal skin development. Developmental dynamics: an official publication of the American Association of Anatomists, 227(2), 192-202.
27. J. A. Mack, L. Li, N. Sato, V. C. Hascall and E. V. Maytin: Hoxb13 Up-regulates Transglutaminase Activity and Drives Terminal Differentiation in an Epidermal Organotypic Model. Journal of Biological Chemistry, 280(33), 29904-29911 (2005).
28. Chung, N., Jee, B. K., Chae, S. W., Jeon, Y. W., Lee, K. H., & Rha, H. K. (2009). HOX gene analysis of endothelial cell differentiation in human bone marrow-derived mesenchymal stem cells. Molecular biology reports, 36(2), 227-235.
29. International Agency for Research on Cancer, & World Health Organization. (2018). GLOBOCAN 2012: Cervical Cancer-Estimated Incidence, Mortality and Prevalence Worldwide in 2012.
30. Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., ... & Bray, F. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer, 136(5), E359-E386.
31. Jemal, A., Murray, T., Ward, E., Samuels, A., Tiwari, R. C., Ghafoor, A., & Feuer, E. J. (2005). T. MJ.: Cancer statistics, 2005. CA Cancer J Clin, 55(1), 30.
32. Hassen, W. A., Karsan, F. A., Abbas, F., Beduk, Y., El-Khodary, A., Ghosn, M., ... & Srinivas, S. (2010). Modification and Implementation of NCCN Guidelines™ on Prostate Cancer in the Middle East and North Africa Region. Journal of the National Comprehensive Cancer Network, 8(Suppl_3), S-26.
33. Hariharan, K., & Padmanabha, V. (2016). Demography and disease characteristics of prostate cancer in India. Indian journal of urology: IJU: Journal of the Urological Society of India, 32(2), 103.
34. Feldman, B. J., & Feldman, D. (2001). The development of androgen-independent prostate cancer. Nature Reviews Cancer, 1(1), 34-45.
35. Agus, D. B., Cordon-Cardo, C., Fox, W., Drobnjak, M., Koff, A., Golde, D. W., & Scher, H. I. (1999). Prostate cancer cell cycle regulators: response to androgen withdrawal and development of androgen independence. Journal of the National Cancer Institute, 91(21), 1869-1876.
36. Denmeade, S. R., Lin, X. S., & Isaacs, J. T. (1996). Role of programmed (apoptotic) cell death during the progression and therapy for prostate cancer. The prostate, 28(4), 251-265.
37. Leewansangtong, S., Soontrapa, S., & Tantiwong, A. (1999). Is prostate-specific antigen still the best tumor marker for prostate cancer?. Journal of the Medical Association of Thailand Chotmaihet Thangphaet, 82(10), 1034-1040.
38. Jung, C., Kim, R. S., Zhang, H. J., Lee, S. J., & Jeng, M. H. (2004). HOXB13 induces growth suppression of prostate cancer cells as a repressor of hormone-activated androgen receptor signaling. Cancer research, 64(24), 9185-9192.
39. Breyer, J. P., Avritt, T. G., McReynolds, K. M., Dupont, W. D., & Smith, J. R. (2012). Confirmation of the HOXB13 G84E Germline Mutation in Familial Prostate CancerHOXB13 and Familial Prostate Cancer. Cancer epidemiology, biomarkers & prevention, 21(8), 1348-1353.
40. Muthusamy, V., Duraisamy, S., Bradbury, C. M., Hobbs, C., Curley, D. P., Nelson, B., & Bosenberg, M. (2006). Epigenetic silencing of novel tumor suppressors in malignant melanoma. Cancer research, 66(23), 11187-11193.
41. Jerevall, P. L., Jansson, A., Fornander, T., Skoog, L., Nordenskjöld, B., & Stål, O. (2010). Predictive relevance of HOXB13 protein expression for tamoxifen benefit in breast cancer. Breast Cancer Research, 12(4), 1-8.