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REVIEW

HOXB13 in cancer development: molecular mechanisms and clinical implications

Jian Zhang[1,2,3,*], Ying Ju Li[4,*], Bo Peng[5,*], Xuna Yang[6], Miao Chen[7], Yongxing Li[2,3], Hengbin Gao (✉)[8,9], Haitao Li (✉)[5], Ji Zheng (✉)[2,3]

[1]Department of Otolaryngology & Head and Neck Surgery, General Hospital of Xinjiang Military Command, Urumqi 830000, China; [2]Department of Urology, Urologic Surgery Center, Xinqiao Hospital, Third Military Medical University (Army Medical University), Chongqing 400037, China; [3]State Key Laboratory of Trauma and Chemical Poisoning, Third Military Medical University (Army Medical University), Chongqing 400042, China; [4]State Key Laboratory of Herbage Improvement and Grassland Agro-ecosystems; College of Pastoral Agriculture Science and Technology, Lanzhou University, Lanzhou 730020, China; [5]State Key Laboratory of Molecular Oncology, Beijing Frontier Research Center for Biological Structure, School of Basic Medical Sciences, Tsinghua University, Beijing 100084, China; [6]Tai'an Maternal and Child Health Care Hospital, Tai'an 271000, China; [7]Affiliated Hospital of Traditional Chinese Medicine, Xinjiang Medical University, Urumqi 830000, China; [8]Harry Perkins Institute of Medical Research, QEII Medical Centre and Centre for Medical Research, The University of Western Australia, Perth WA 6009, Australia; [9]ARC Centre of Excellence in Plant Energy Biology, School of Molecular Sciences, The University of Western Australia, Perth WA 6009, Australia

Abstract **The transcription factor HOXB13 plays crucial roles in cancer development. HOXB13 is abnormally expressed in most cancers, which makes it a valuable therapeutic target for cancer therapy. The level of HOXB13 differs significantly between healthy and cancer tissues, which indicates that the level of HOXB13 is closely related to carcinogenesis. The regulatory network mediated by HOXB13 in cancer proliferation, metastasis, and invasion has been systematically investigated. Moreover, *HOXB13* variants play distinct roles in different cancers and populations. By understanding the molecular mechanisms and mutation features of HOXB13, we provide a comprehensive overview of carcinogenesis networks dependent on HOXB13. Finally, we discuss advancements in anticancer therapy targeting HOXB13 and the roles of HOXB13 in drug resistance to molecular-targeted therapies, which serves as a foundation for developing HOXB13-targeted drugs for clinical diagnosis and cancer therapies.**

Keywords HOXB13; carcinogenesis; epigenetic regulation; SNPs; clinical treatment

Introduction

HOXB13 belongs to the B subtype of the HOX protein family, and it functions as a transcriptional regulatory factor involved in organogenesis and embryogenesis [1–3]. The homeodomain of HOXB13 contains three alpha helices, namely, α1, α2, and α3, where α3 could be embedded in the major groove of dsDNA to interact with the specific DNA sequence of CAATAAA [4]. The aberrant expression of HOXB13 promotes different cancers. For example, the upregulation of HOXB13 is associated with the development and progression of endometrial cancer (EC) [5], melanoma [3], lung cancer [6,7], ependymoma [8], glioma [9], and nasopharynx cancer [10]. Lowered HOXB13 expression is associated with colorectal cancer development [11,12]. Notably, HOXB13 functions as an oncogenic factor and anticancer factor, which is involved in the development and progression of prostate cancer (PCa) [13–16], gastric cancer (GC) [17,18], and breast cancer (BC) [5,19,20]. In addition, recent studies have shown that somatic mutations of *HOXB13* are intimately associated with carcinogenesis and cancer progression [21–23].

The transcription of HOXB13 is regulated by epigenetic machineries including DNA methylation and histone acetylation [24–26]. HOXB13 could regulate transcription of target genes through recognizing specific DNA sequences and recruiting cofactors to the DNA

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Correspondence: Hengbin Gao, hengbin.gao@uwa.edu;
Haitao Li, lht@tsinghua.edu.cn;
Ji Zheng, jizheng023@aliyun.com

*These authors contributed equally to this study.

complexes participating in carcinogenesis [27]. For example, Yin *et al*. [28] reported that HOXB13 could stably recognize methylated CpG through a direct hydrophobic interaction between the amino acid and 5-methyl group of both methylcytosines of the CpG dinucleotide in various physiologic environments. In clinical research, HOXB13 is consistently considered a crucial molecular marker for carcinogenesis, cancer progression, and prognosis. Thus, it is generally recognized as an important therapeutic target for designing novel antineoplastic agents. Several studies have found that numerous small molecule compounds targeting HOXB13 could effectively inhibit cancer [29–31].

Although the molecular functions of HOXB13 have been widely studied in carcinogenesis, a systematic summary of HOXB13 is lacking. HOXB13 may be an important point for applying molecular therapy by integrating theoretical research.

Regulation of *HOXB13* at the transcriptional level in cancers

Epigenetic modifications are involved in cancer development, proliferation, metastasis, and invasion through regulating *HOXB13* expression [32–34].

Histone modification

BRD4, which is a key member of the Bromodomain and extra-terminal (BET) families, binds to the BRAH1 (−799 bp) and BRAH2 (−268 bp) sites of the *HOXB13* promoter. It promotes the acetylation of histone H3K27, H4K5, and H4K8 at the *HOXB13* locus, which further upregulates HOXB13 expression. The increased expression of *HOXB13* results in PCa development and metastasis by promoting cell cycle, DNA damage response, nucleotide metabolism, and metastasis [29,35] (Fig. 1-①). The transcription cofactor EZH2 and lncRNA

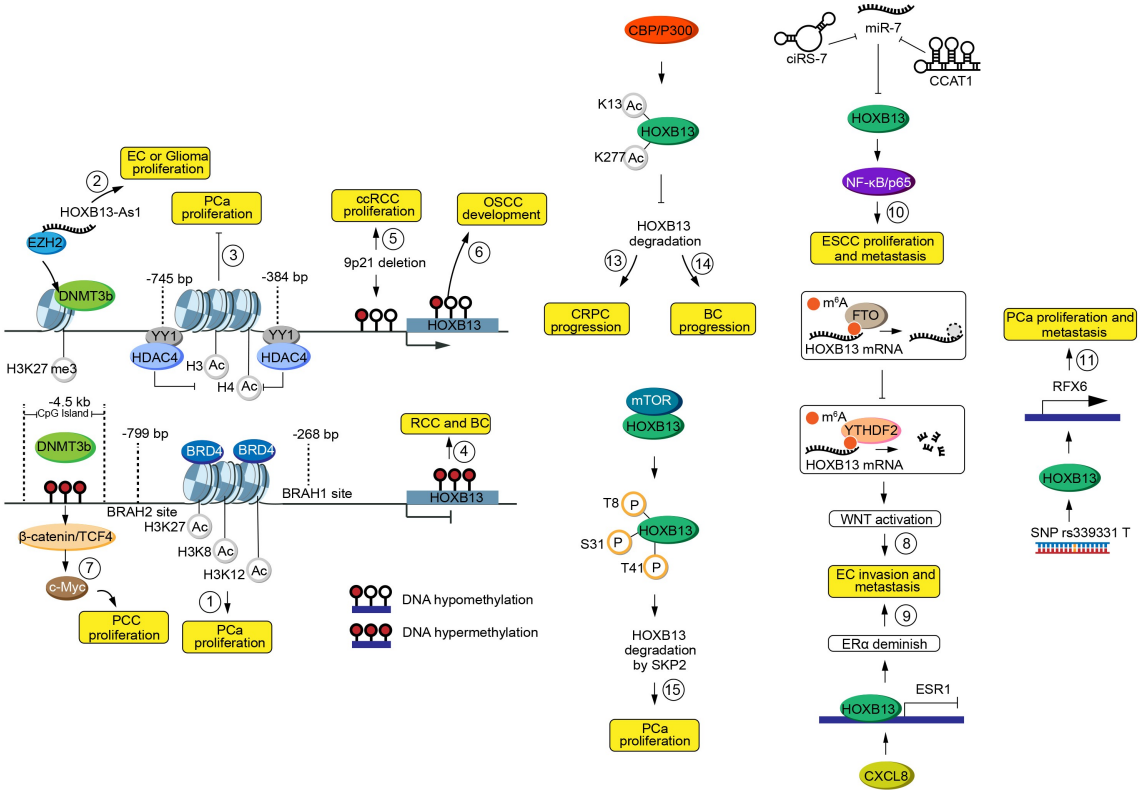

Fig. 1 Regulation of HOXB13 at post-transcriptional, post-translational, and translational levels during carcinogenesis. BRD4 combines with the BRAH1 and BRAH2 sites of the HOXB13 promoter to activate gene transcription. EZH2, YY1, and HDAC4 could inhibit HOXB13 transcription by mediating HOXB13 histone modification. In addition, the methylation of CPG 5' CpG islands and ~4.5 kb islands affects HOXB13 transcription. These epigenetic changes are involved in carcinogenesis through regulating HOXB13 expression. For the transcriptional product mRNA produced after HOXB13 transcription, FTO could increase the demethylation modification in the 3' UTR sequence of HOXB13 mRNA. This phenomenon promotes the translation of mRNA products, activates the WNT signaling pathway, and ultimately leads to cancer progression. After HOXB13 synthesis, CXCL8 could stimulate cancer progression by facilitating the specific binding of HOXB13 to the ESR1 promoter. Certain miRNA inhibitors such as CCAT1, and ciRS-7 increase HOXB13 expression by suppressing miR-7 or miR-17-5p, which stimulates cancer progression. Moreover, the SNP rs339331 variant at 6q22 could stimulate HOXB13 to bind to activated *cis*-regulatory elements, which in turn promote the proliferation and metastasis of cancer cells. Pointed lines indicate promotion, and flat-ended lines represent inhibition.

HOXB13-AS1 provide an inhibitory signal to suppress *HOXB13* expression through enhancing the trimethylation of histone H3 at lysine 27 (H3K27me3) of the *HOXB13* promoter, which results in EC or glioma progression [9,36,37] (Fig. 1-②). Furthermore, the multifunctional zinc-finger transcription factor Yin Yang1 (YY1) could recruit histone deacetylase 4 (HDAC4) to the two YY1 binding sites at −384 and −745 bp of the *HOXB13* promoter; this recruitment represses *HOXB13* expression to inhibit PCa through reducing histone H3 and histone H4 acetylation and altering the local chromatin structure [30,38] (Fig. 1-③).

DNA methylation

DNA methylation of CpG islands in the promoter could largely repress *HOXB13* transcription and induce *HOXB13*-related carcinogenesis [25,26]. Actually, the hypermethylated *HOXB13* in RCC cell lines exhibits strong transcription inhibition and contributes to microvascular invasion and cancer cell proliferation [34] (Fig. 1-④). However, in another subtype of RCC (called clear cell renal cell carcinoma), the CpG islands of the *HOXB13* promoter were hypomethylated, which activated the *HOXB13* (Fig. 1-⑤). The diverse results of these studies suggest that hypermethylation and hypomethylation at 5' CpG islands contribute to the formation of renal carcinoma. This contribution is mainly attributed to the different roles of *HOXB13* during the development of renal carcinoma [39]. In addition, the increased *HOXB13* caused by the hypomethylation of 5' CpG islands correlates with increased risk for oral squamous cell carcinoma (Fig. 1-⑥) [40]. Considerable attention has been given to understanding why the 5' CpG islands of *HOXB13* are prone to hypermethylation. Some studies have revealed that hormone receptors may be a key factor in *HOXB13* demethylation. For example, Pilato *et al*. [41] observed that the methylated 5' CpG islands of *HOXB13* are more likely to induce lymph node metastasis and cancer proliferation in estrogen receptor (ER)-positive BC patients compared with ER-negative BC patients (Fig. 1-④). However, additional corresponding mechanisms should be explored in greater detail.

Certain novel CpG islands at ~4.5 kb upstream of the *HOXB13* transcription start site were identified from *HOXB13*-dependent proximal colon cancer (PCC) [18,42]. However, whether these novel CpG islands could trigger PCC progression is unclear (Fig. 1-⑦). Identifying the accurate site of CpG islands and their role in regulating carcinogenesis will be a valuable challenge for future research.

Overall, diverse epigenetic modifications not only directly regulate *HOXB13* transcription levels and lead to carcinogenesis but also co-regulate *HOXB13* transcription together with other transcription factors. In clinical settings, targeting modification sites or catalytic proteins is expected to be an effective strategy for treating cancers with high *HOXB13* expression.

Regulation of *HOXB13* at the post-transcriptional and translational levels in cancers

A type of m^6A demethylase in eukaryotic mRNA, which is known as Fe II/αKG-dependent dioxygenase AlkB protein (FTO), can catalyze demethylation in the 3' untranslated region (3' UTR) of *HOXB13* mRNA, which results in decreased *HOXB13* mRNA decay and *HOXB13* upregulation. Ultimately, the increased HOXB13 level induces the upregulation of target proteins c-myc, snail, MMP2, MMP7, and MMP9 through activating the WNT signaling pathway, which in turn leads to the metastasis and invasion of EC [43] (Fig. 1-⑧). Furthermore, some bioactive factors, including CXCL8 [5] (Fig. 1-⑨), lncRNA-colon cancer associated transcript-1 (CCAT1) [44], the sponge for miR-7 named ciRS-7 [45] (Fig. 1-⑩), and SNP rs339331 variant allele T at 6q 22 [46] (Fig. 1-⑪), could directly or indirectly increase the expression of HOXB13, which activates the HOXB13-targeted genes associated with the development and progression of cancers (such as EC [5], EScc [45], and PCa [46]). Overall, various post-transcriptional and post-translational modifications are involved in regulating the protein stability and DNA binding activity of HOXB13.

Interacting factors of HOXB13 in cancers

HOXB13 could interact with various factors to promote cancer development. Among these factors, the interaction between HOXB13 and AR or MEIS1 plays critical roles in carcinogenesis.

AR

AR is a ligand-dependent nuclear transcription factor and belongs to steroid hormone receptor superfamilies. AR contains an N-terminal domain, a DNA binding domain, and a C-terminal ligand binding domain [29,47]. AR-HOXB13 has carcinogenic and anticancer effects on carcinogenesis. First, AR-HOXB13 could inhibit the transcriptional activity of AR through a feedback mechanism, which in turn inhibits the expression of AR target gene *NKX3.1* and subsequently induce the suppression of PCa growth [48,49] (Fig. 2-①). Second, AR-HOXB13 could stimulate the proliferation, migration, and adipogenesis of androgen-dependent PCa by activating or inhibiting the transcription of different AR target genes. For example, AR-HOXB13 could inhibit the expression of HOXB13-independent *PSA*, *STEAP4*, and *FASN* by preventing AR from binding to chromatin,

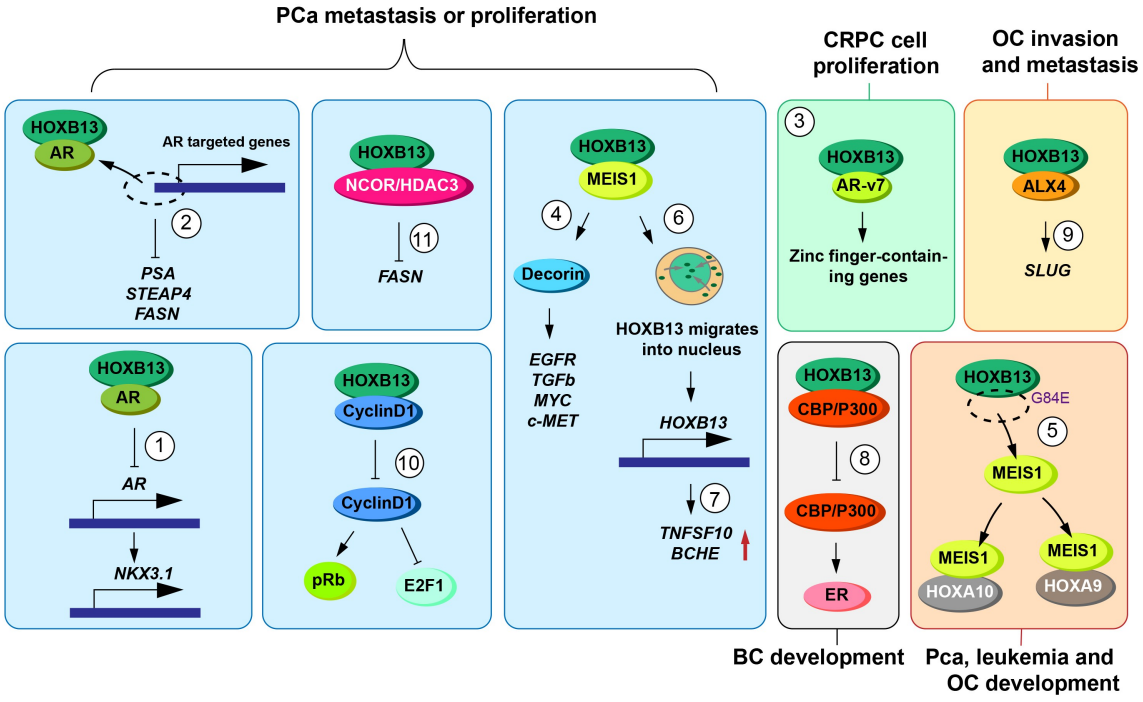

Fig. 2 HOXB13 interacts with various factors to promote cancer development. HOXB13 could interact with AR, AR-V7, MEIS1, cyclin D1, and NCOR/HDAC3 to activate the expression of target genes or the downstream pathways, which results in cancer proliferation or metastasis. The interaction of HOXB13 with CBP/p300 could activate the ER signal pathway and then promote the progression of BC. In addition, HOXB13 could interact with ALX4 to increase SLUG expression, which leads to OC invasion and metastasis. Pointed arrows indicate promotion, and flat-ended arrow represent repression.

which promotes PCa development [50] (Fig. 2-②). These contrary findings on cancer phenotypes may be attributed to the different binding ways of AR to HOXB13. The exact mechanism deserves further study. Moreover, AR-V7 belonging to the splicing variant of AR could colocalize with HOXB13 and then upregulates AR target oncogenes (such as zinc-finger-containing genes) by unfolding the chromatin of the castration-resistant prostate cancer (CRPC) genome, which results in the proliferation of CRPC cells [47,51] (Fig. 2-③).

The interaction between HOXB13 and AR could be physically disrupted by micro-molecules. For example, the cancer risk-associated SNP rs12773833 could inhibit the expression of the AR target gene *TMEM180* by disturbing the binding of AR to HOXB13 at 10q24.32. Therefore, developing the methods to separate AR-HOXB13 will provide a new direction for treating PCa [48].

MEIS1

MEIS is a member of Triamino Acid Ring Extension (TALE) protein family and contains three analogs, namely, MEIS1, MEIS2, and MEIS3 [52]. MEIS1 and MEIS2 are essential transcription factors that play important roles in regulating cell differentiation pathway during cell growth [53]. As normal prostate tissue progresses to primary tumor and eventually to metastasis, the expression of MEIS1 and MEIS2 gradually decreases. MEIS1 and MEIS2 are also considered to be prognostic markers for PCa. Higher expression levels of MEIS1 and MEIS2 result in a better disease prognosis for PCa [53]. Research also indicates that the overexpression of MEIS1 and MEIS2 could prevent tumor cells from stagnating in the G0/G1 phase and reduce the number of S-phase cells, which inhibit the proliferation and metastasis of PCa cells [54,55]. At present, few studies are available on the impact of MEIS3 on the occurrence and development of PCa. Only a limited number of works have shown that the expression level of MEIS3 in PCa is very low, which makes it nearly undetectable [56].

The expression pattern of HOXB13 is similar to that of MEIS1, and the tumor inhibitory activity of MEIS1 depends on HOXB13. HOXB13 contains two highly conserved MEIS binding domains located in the exon region, which can recruit MEIS1 [52]. Thus, the HOXB13 protein can interact with MEIS1 through its conserved MEIS binding domain in a DNA-independent manner, which forms a heterodimer [56]. Owing to the diversity of MEIS1–HOXB13 functions, MEIS1–HOXB13 may play dual roles in carcinogenesis, and the dual roles of MEIS1–HOXB13 is mainly reflected in the occurrence and progression of PCa. MEIS1–HOXB13 suppresses the development of PCa through two primary

mechanisms. On the one hand, MEIS1–HOXB13 inhibits the cell proliferation of PCa by regulating extracellular proteoglycans, particularly the RTK inhibitor Decorin, to activate key tumor suppressor factors in the carcinogenic pathway such as *EGFR*, *TGFb*, *MYC*, and *c-MET* [52] (Fig. 2-④). On the other hand, MEIS1–HOXB13 prevents the translocation of AR from the cytoplasm to the nucleus and hinders its recruitment to the promoter and enhancer of *PSA*. This phenomenon effectively blocks the transcriptional activity of AR and impedes the progression of PCa [27,57]. The MEIS1–HOXB13 complex drives the cell proliferation of PCa through four potential carcinogenic mechanisms. First, the stability of HOXB13–MEIS1 is high under normal conditions. However, this condition can be disrupted by mutations in *HOXB13*. These mutations predominantly occur within the two conserved domains at the N terminus of HOXB13 that serve as MEIS1 binding platforms, which result in the release of free MEIS1. Subsequently, the free MEIS1 forms complexes with either HOXA9 or HOXA10, which promote the progression of PCa and leukemia and ovarian cancer [52,56] (Fig. 2-⑤). Second, the MEIS1–HOXB13 complex could help HOXB13 shuffle and amplify in nucleus, which also enhance its DNA binding activity. The complex prolongs the half-life of HOXB13, increases its transcriptional activity, and promotes its role HOXB13 in stimulating cell proliferation and gene regulation during carcinogenesis [56] (Fig. 2-⑥). Third, MEIS1–HOXB13 could induce PCa by inhibiting the expression of cancer suppressor genes, such as *BCHE* and *TNFSF10* [56] (Fig. 2-⑦). Fourth, HOXB13–MEIS1 heterodimers have the potential to bind to methylated DNA promoters. This binding can silence cancer suppressor genes or affect critical signaling critical pathways associated with carcinogenesis. These combined factors may contribute to the development and progression of PCa [58].

HOXB13 could also interact with CBP/p300 [59] (Fig. 2-⑧), aristaless-like homeobox 4 (ALX4) [60] (Fig. 2-⑨), cyclin D1 [61] (Fig. 2-⑩), and histone deacetylases 3 (NCOR/HDAC3) [25] (Fig. 2-⑪) to activate the expression of target genes or the downstream pathways, which results in cancer progression (such as BC [59], OC [60], and PCa [61]). These new findings are important for exploring carcinogenesis and cancer targeting therapy. Future molecular targeted therapy should prioritize HOXB13-interacting proteins [62].

HOXB13 functions as a transcription factor in cancer

In cancer proliferation, HOXB13 could increase target gene expression by directly binding to the promoter of *HOXC-AS3* [63] (Fig. 3-①) and *ESR1* [5] (Fig. 3-②), which results in glioma cells [63] and EC cells proliferation [5], respectively. HOXB13 could activate the RB/E2F1 pathway (Fig. 3-③) or the JNK/c-Jun signaling pathway (Fig. 3-④) through regulating the target genes of p21, which triggers the proliferation of PCa [64,65].

In cancer invasion and metastasis, HOXB13 could upregulate *IGF-1R* expression by activating the PI3K/AKT/mTOR signaling pathway, which causes the promotion of the metastasis and invasion of GC cells [33] (Fig. 3-⑤). By contrast, overexpressed *HOXB13* inhibits the Hippo signaling pathway involved in TEA domain transcription factor 4 (TEAD 4) by activating its downstream target gene *VGLL4*. This suppression of the Hippo pathway leads to reduced metastasis and invasion of GC [17] (Fig. 3-⑥). HOXB13 could also activate the AKT/mTOR signaling pathway by promoting *IL-6* transcription, which results in BC invasion [20] (Fig. 3-⑦). In PCa, HOXB13 could increase invasion and metastasis by upregulating *PDEF* expression [66] (Fig. 3-⑧), downregulating *CCL2* and *IBSP* expression [67] (Fig. 3-⑨), or stimulating intracellular zinc transport to extracellular [68] (Fig. 3-⑩).

In general, HOXB13 could provide inflammatory microenvironments for the occurrence of EMT during the malignant transformation of normal-functioning cells and increase the self-renewal ability of cancer cells by regulating various target genes or target proteins [60,69,70]. Therefore, future studies should prioritize identifying downstream targets of HOXB13 under pathophysiologic conditions and exploring the carcinogenic mechanisms mediated by HOXB13. These efforts will pave the way for the application of cancer-targeting drugs.

Post-translational modifications of HOXB13 in cancer

Multiple post-translational modifications of HOXB13 are involved in carcinogenesis and cancer progression. Recently, a novel lysine 13 (K13) acetylation in the N terminus of HOXB13 mediated by CREB binding protein/adenoviral E1A binding protein of 300 kDa (CBP/p300) histone acetyltransferase, is found to be involved in upregulating *HOXB13* expression; this upregulation in turn promotes the progression of CRPC [71,72] (Fig. 1-⑬). The acetylation of HOXB13 at K277 mediated by p300 could prevent HOXB13 from degradation and coactivate HOXB13 in inducing BC progression [19] (Fig. 1-⑭). In addition, mTOR could directly interact with HOXB13 and phosphorylate it at threonine 8, threonine 41, and serine 31. The phosphorylated HOXB13 is then polyubiquitinated by E3 ligase SKP2 and subsequently degraded, which ultimately

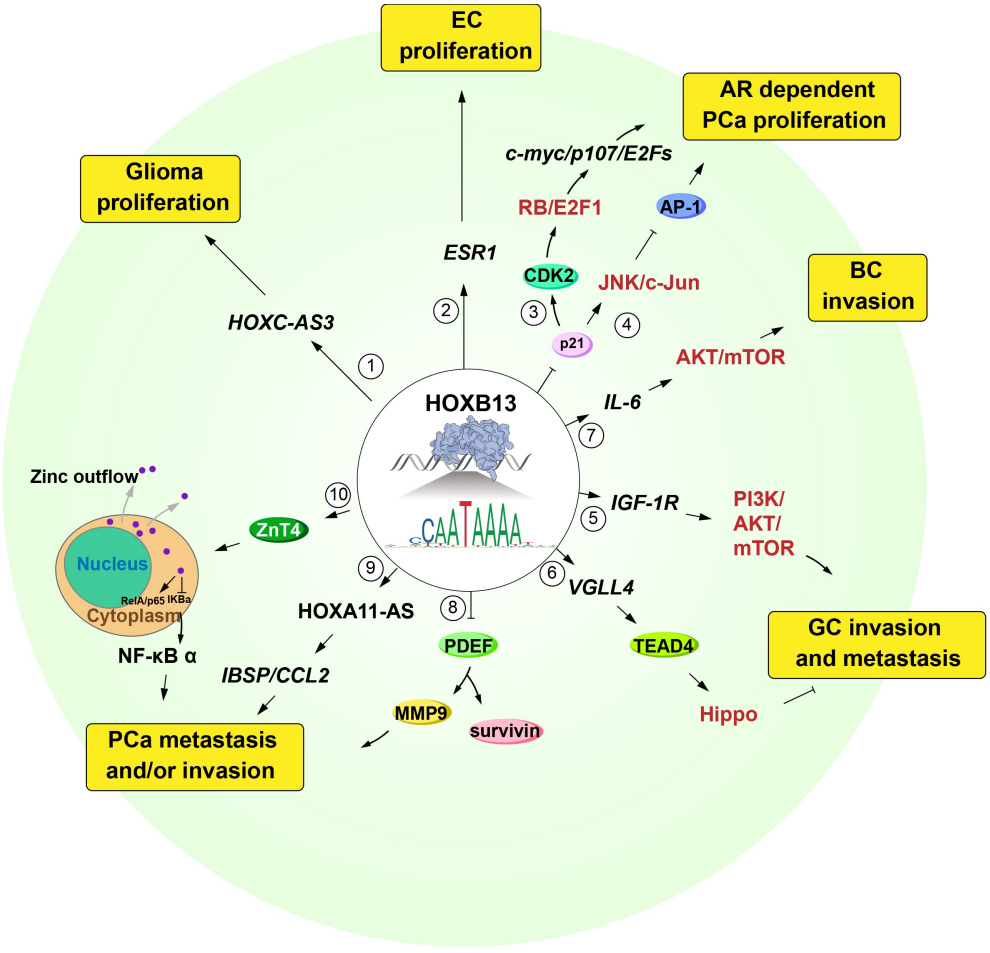

Fig. 3 Roles of HOXB13 as a transcription factor in carcinogenesis. HOXB13 is involved in cancer proliferation and metastasis by directly regulating target genes such as *HOXC-AS3* and *ESR1*, or indirectly activating the RB/E2F1 pathway or the JNK/c-Jun signaling pathway through regulating the target genes of p21. In addition, HOXB13 activates downstream signaling pathways by increasing the expression of IL-6, IGF-1R, and VGLL4, which in turn stimulates cancer proliferation and metastasis. Moreover, HOXB13 is involved in cancer proliferation and metastasis by indirectly activating the target proteins, target genes, and signaling pathways of certain protein factors such as PDEF, HOXA11-AS, and ZnT4. Pointed arrows indicate positive regulation, and flat-ended arrows represent repressed regulation.

leads to the oncogenic function of HOXB13 in the prostate [73] (Fig. 1-⑮).

Deleterious single nucleotide polymorphisms of HOXB13 involved in cancer progression

SNPs in the coding region

Nearly 50% of the gene mutations associated with hereditary diseases are caused by SNPs in the coding region [74]. Single nucleotide polymorphisms (SNPs) in the coding region are well known to be deleterious or pathogenic because they could disrupt protein sequences, microstructure, and functions due to missense and frameshift mutations [75]. *HOXB13* locates on human chromosome 17q21.32 and consists of two MEIS domains (a.a 80–91 and 136–146) and a homeodomain (a.a 216–275). Some studies revealed that most SNPs in *HOXB13* could impair its structure (Fig. 4A), which causes carcinogenesis [21,23].

Among these deleterious SNPs, seven SNPs occurring in the MEIS domain of *HOXB13* [22,76,77]. G84E, Y80C, Y88D, and L144P could induce PCa by breaking the binding domain of HOXB13 [22,25,53]. G84E could prolong the half-life of HOXB13 by affecting the MEIS domain, and it change the expression of target genes through disrupting the binding activity of HOXB13. Consequently, G84E could activate *RFX6* and be expressed over a longer period of time. Y80C could disrupt the structure of HOXB13 by affecting the MEIS domain, which reduces HOXB13 stability and represses HOXB13 transcriptional activation for genes related to cell cycle regulation and proliferation [22]. G84E, L144P, and Y88D could disturb the transcriptional regulation of

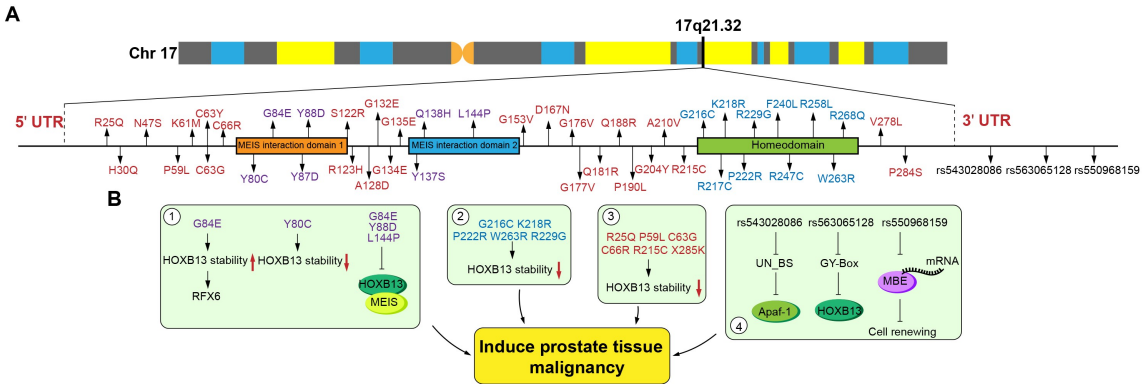

Fig. 4 (A) Genomic location, domains, and mutations of HOXB13 in human patients. HOXB13 consists of 284 amino acids, two MEIS binding domains, and a single DNA binding homeobox domain. Clusters of variants can be observed within or nearby the two MEIS binding domains and the homeodomain. (B) Distribution characteristics of HOXB13 mutations in coding and noncoding regions. In the coding region, the G84E, L144P, Y80C, and Y88D mutations in the MESI domain are involved in carcinogenesis by affecting the HOXB13 stability or disturbing the binding of HOXB13 to MEIS. The mutations occurring in the homeodomain, including P222R, G216C, W263R, K218R, and R229G, are involved in prostatic carcinogenesis by disrupting the structure of the HOXB13 homeodomain. In addition to the mutations occurring in the MEIS domain and homeodomain, some other loci variants such as P59L, R25Q, C63G, C66R, R215C, and X285K are also involved in carcinogenesis by regulating HOXB13 stability. Moreover, rs543028086, rs563065128, and rs550968159 in the noncoding region are closely associated with carcinogenesis. Red color labels the mutations located in the noncoding region, and blue words label the mutation sites in the homeodomain.

MEIS1/HOXB13 on cancer suppressor genes by repressing the affinity of HOXB13 for MEIS1 [25,53] (Fig. 4B-①). In addition, 10 SNPs are positioned in the homeodomain [78–80]. Many SNPs including P222R, G216C, W263R, K218R, and R229G could weaken the stability of HOXB13, change the binding pattern of HOXB13 to DNA, and induce the aberrant expression of target genes, which eventually lead to PCa development [78,79] (Fig. 4B-②).

In addition to the SNPs located in the MEIS domain and homeodomain, 27 SNPs could affect the stability and function of HOXB13 [22,77,78,80,81]. P59L, R25Q, C63G, C66R, and R215C are believed to reduce the stability of HOXB13 by affecting HOXB13–DNA binding [22]. X285K could continuously induce translation due to loss of a stop codon, which results in a 34% elongation of the HOXB13 and extends HOXB13 by 96 amino acids (Fig. 4B-③). As a result, aberrant HOXB13 and prostate carcinogenesis are generated [77].

SNPs in the noncoding region

The SNPs located in the 3' UTR of *HOXB13* could impair HOXB13-mediated gene expression and biological function. To date, three SNPs in the noncoding region of the 3' UTR have been identified as being involved in carcinogenesis. SNP rs543028086 could positively regulate PCa proliferation by disrupting the RNA chaperone UNR binding site (UN_BS) motif and inhibiting the pro-apoptotic factor Apaf-1. SNP rs563065128 could disturb the renewal process of stem cells by deleting the Mushashi Binding Element (MBE, a type of mRNA binding protein) UTR motif in *HOXB13*. It could also prevent injured cells from being replenished by local stem cells and increase the potential risk of carcinogenesis. SNP rs550968159 could induce the loss of specific GY-Box pattern in the 3' UTR noncoding region of *HOXB13*, which avoids the probability of translational suppression of HOXB13 and leads to *HOXB13* expression disorder [22] (Fig. 4B-④). These SNPs are all involved in the malignant transformation of prostate.

Geographical distribution of *HOXB13* mutations

Although the frequency of *HOXB13* mutations is very low across the general population, carriers of *HOXB13* mutations have a high risk of developing cancers [81–84]. Many studies have reported that *HOXB13* mutations are an important factor in carcinogenesis. Among the various mutations of *HOXB13*, the G84E mutation is the most widely studied. The G84E mutation has been widely observed in the carcinogenesis of different organs. Numerous works have shown that G84E is involved in the development and progression of leukemia, bladder cancer, BC, renal cancer, non-Hodgkin's lymphoma, and colon cancer [3,9,80,85–87]. A study in 2020 reported that G84E was identified in PCa, non-melanoma skin cancer, and rectosigmoid cancer among 20 collected cancer tissues, which suggests that G84E belongs to a potential pathogenic factor for carcinogenesis [3]. Laitinen *et al*. [88] observed a significant correlation between G84E and BC development, which reveals that G84E is a potential carcinogenic factor. Current research on G84E is mainly focused on its roles in the development of PCa, especially in familial inherited PCa.

Studies have demonstrated that approximately 66% of G84E carriers have a family history of PCa, and G84E carriers tend to develop PCa at an earlier age compared with non-carrier [81,89].

Several studies have reported that the *HOXB13* mutations are closely related to geographical distribution [84, 90]. Statistical analysis has revealed that the G84E mutation is predominantly prevalent among Northern Europeans, with a carrier rate of 1.06%. By contrast, Western Europeans and North Americans display carrier rates of 0.60% and 0.31%, respectively, which indicate significant geographic disparities [91]. In the Nordic countries, the highest rate of G84E is found in the population of Finland, where the carrier frequency could increase to 3.5% across all ages (Fig. 4C-①). In particular, for the people with familial hereditary PCa, the G84E carrier rate could reach 8.4% [92]. In Sweden, the carrier rate of G84E was found to be 10.3% among individuals aged between 35 and 55 years old; moreover, the risk of developing PCa could be increased to 33% by the time they reached the age of 80 [93]. In Western European countries like the UK, the frequency of G84E carriers in healthy population ranges from 0.1% to 0.6%, while it is approximately at a frequency of 1.5% in PCa patients [89]. In the United States of America, the G84E variant is predominantly observed in individuals of European descent, particularly those with Nordic and Western European ancestry. The frequency of G84E carriers among European descent PCa patients in the United States population is approximately 1.3% [79]. Conversely, the occurrence of G84E carriers within the Asian population is minimal. A study conducted on PCa patients in China revealed that only 3 out of 671 individuals were identified as G84E carriers, which suggests that the G84E mutation contributes less to the genetic risk of PCa in Asian populations [94]. Studies on the frequency of G84E carriers in the general population in Africa, Latin America, and some other regions are relatively limited. Some works have suggested that the frequency of G84E carriers in African and Latin American populations may be intermediate between Caucasian and Asian populations, and more research is needed to clarify its distribution in these populations [91, 95]. Considering the geographical characteristics of G84E, a view suggested that G84E carriers actually share a common haplotype, which originates from Northern Europeans [92]. The Nordic Caucasian population has been the subject of studies that have demonstrated a significantly lower overall survival rate among G84E carriers compared with G84E non-carriers. In addition, an increased recurrence rate and invasion ability of PCa are observed in G84E carriers as opposed to G84E non-carriers [96]. The hypothesis suggests that the spread of G84E may have originated from Finland and extended to other countries. This spread can be attributed to the migration of approximately 700 000 Finns to Sweden, United States, and Canada between 1866 and 1970 [97]. These findings suggest that the geographic distribution of the G84E is not uniform, with significant variations in the frequency of G84E carriers among different racial populations. In populations of European descent, the frequency of G84E carriers is higher than in African and Asian descent. These differences reflect the complexity and diversity of genetic risk for PCa, which emphasize the importance of personalized prevention and screening for PCa in different populations. The Philadelphia Prostate Cancer Consensus recommends that any male with *HOXB13* mutation should underwent prostate-specific antigen analysis no later than 40 years old for early diagnosis and treatment [98]. Therefore, regular risk screening for PCa should be considered for individuals carrying the G84E mutation and having a family history of PCa, regardless of their ethnic background. This proactive approach is essential in preventing the development of PCa and significantly contributes to clinical strategies [99].

Some other *HOXB13* SNPs are also significantly correlated with carcinogenesis and exhibit evident heterogeneity in geographical distribution [100–102]. Germline mutations P190L, R217C, and R268Q of *HOXB13* are closely related to BC development. P190L is most common in Africans but absent in Asians. R217C and R268Q are exclusively found in Europeans and have no any presence in Asians and Africans [80]. Moreover, germline mutations G135E, G132E, A128D, F240L, and X285K of *HOXB13* are closely related to PCa development. G135E and G132E are mainly distributed in Chinese and Japanese, respectively [101,103]. A128D and F240L are mainly distributed in Portuguese and Japanese. R229G and G216C are mainly observed in African descent [104], and X285K is found only in men of West African descent [77, 105]. Collectively, analyzing the geographical distribution of *HOXB13* mutations not only show strong linkage with diverse cancer occurrences but also exhibit distinct biases in populations from different regions and ages. These distinct biases suggest that the frequency of *HOXB13* mutation could be a powerful target gene for developing precise probes to predict cancer incidence in specific human populations.

Clinical significances in the treatment and diagnosis of cancers

Differential diagnosis

HOXB13 shows great potential as a biomarker for the early detection of specific cancers. Overexpressed HOXB13 demonstrates high specificity and sensitivity in diagnosing cauda equina paraganglioma and myxopa-

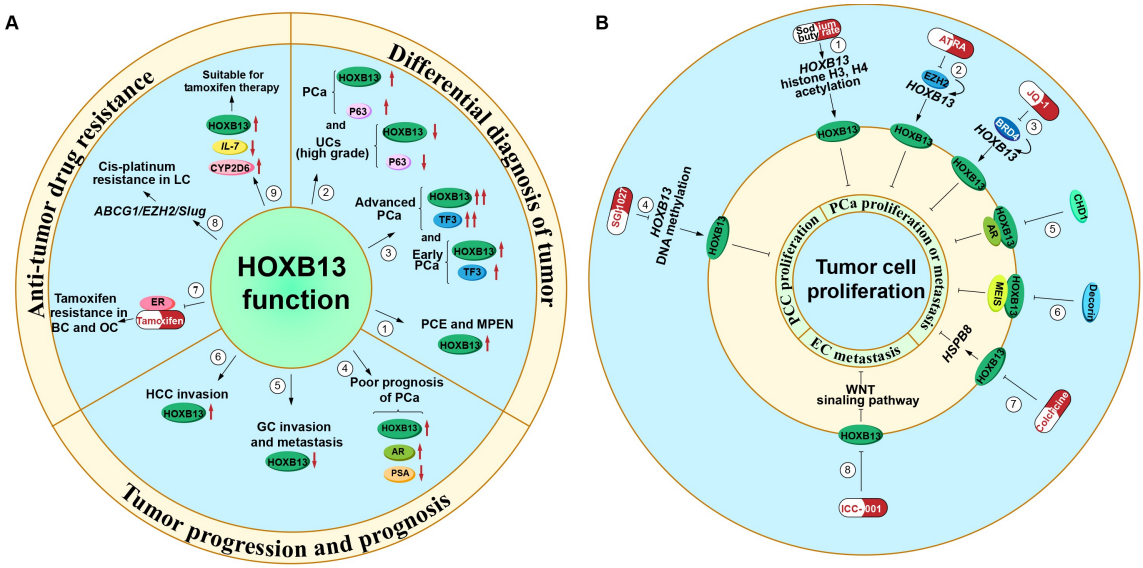

Fig. 5 (A) HOXB13 has demonstrated an incomparable advantage in the differential diagnosis of cancers, predicting drug resistance, and monitoring therapeutic responses. (B) HOXB13 acts as an important target for developing novel anticancer drugs.

pillary ependymoma, which make it valuable for distinguishing the two cancers from other cell-derived neurologic cancers in clinical application [106–108] (Fig. 5A-①). In cervical cancer, HOXB13 is involved in EMT development and could be used as a biomarker to identify cervical cancer metastasis [109]. HOXB13 is overexpressed in malignant BC [110] and laryngeal squamous cell carcinoma [111], which shows important clinical significance for their clinical screening and diagnosis. In addition, several studies have demonstrated that HOXB13 is a sensitive and specific prostate-derived biomarker [13,112,113]. HOXB13 could effectively differentiate PCa from other urothelial cancers [114] and has nearly 100% sensitivity for identifying PCa cells migrate to the brain and colorectum [115–117]. Moreover, combining HOXB13 with other bioactive factors could improve the accuracy of diagnosing PCa and is more suitable for differential diagnosis in clinical settings. This improvement is due to the inherent limitations of a single biomarker, which often exhibits certain rates of false positives and false negatives. Using multiple biomarkers together could address these deficiencies, improve the accuracy of disease diagnosis, and even be used to precisely evaluate the severity of the disease [73,116,118]. For instance, HOXB13/P63 could be applied in distinguishing poorly differentiated PCa from high-grade urothelial carcinoma [73,116] (Fig. 5A-②). The transcriptional level of HOXB13/TFF3 could distinguish the PCa stages. The low expression level of HOXB13/TFF3 labels the primarily PCa, while the high level marks the malignant stage [118] (Fig. 5A-③).

In clinical practice, detecting HOXB13 provides crucial diagnostic information for certain types of cancer. Combining HOXB13 with other biomarkers considerably improves the accuracy of disease diagnosis. However, using HOXB13 alone as a biomarker to predict and diagnose carcinogenesis has some limitations [116,118]. First, although HOXB13 has positive implications for the diagnosis of PCa, it is not an absolutely specific marker. Other factors, such as age, ethnicity, and some other genetic mutations, also affect the development and progression of PCa [79]. Therefore, the diagnosis of PCa should be evaluated in combination with other biomarkers and clinical information. Second, the use of HOXB13 as a biomarker for diagnosing other types of cancer is less well-studied and requires further research. Third, the accuracy and reproducibility of genetic testing technologies are crucial factors affecting the use of HOXB13 as a biomarker in clinical settings. Ensuring the standardization and high quality of testing methods is essential for the clinical application of HOXB13. Overall, HOXB13 has shown great clinical potential as a biomarker in the diagnosis of PCa, but its application in other cancers still needs to be explored. Furthermore, future studies should focus on optimizing the combination of markers with HOXB13 to enhance its clinical application.

Prediction of cancer progression and prognosis

HOXB13 is involved in PCa metastasis and invasion by affecting the expression of mitotic kinase subsets [119] (such as stimulating the expression of *CIT/STK21* kinase and inhibiting the expression of *HSPB8*). Therefore, HOXB13 could be used as a good biomarker for predicting cancer progression and prognosis [61,120–122]. Kwan *et al*. [123] incorporated HOXB13 in a new AR-based polygenic marker in whole blood and observed that their interaction could be used to evaluate

the risk level and prognosis of PCa patients. Zabalza *et al*. [124] discovered that the combination of HOXB13 and PSA or AR could serve as a prognostic predictor of PCa (Fig. 5A-④). Some other studies have reported similar results [119,125,126]. Recent studies have revealed that HOXB13 expression in GC tissues is significantly lower than that in adjacent non-malignant gastric tissues. As HOXB13 expression decreases, the degree of invasion, lymph node metastasis and pathological stage of GC become more severe. Furthermore, the expression of HOXB13 in poorly differentiated GC tissues is significantly lower than that in highly to moderately differentiated GC tissues; the malignant grade of poorly differentiated GC is higher than that of highly to moderately differentiated GC, which suggests that GC with low HOXB13 expression has a higher degree of malignancy (Fig. 5A-⑤). Therefore, low HOXB13 expression could serve as an indicator of GC progression and prognosis [127]. Interestingly, in hepatocellular carcinoma (HCC), the expression level of HOXB13 in lesions is significantly higher than that in surrounding non-cancer tissues. The expression level of HOXB13 is proportional to the invasion grade, pathological stage, and overall survival rate of HCC patients (Fig. 5A-⑥), which implies that high expression of HOXB13 is an indicator of HCC progression [128].

Prediction of drug resistance and effects of drug treatment

Tamoxifen is a classical antiestrogen drug that could compete with estradiol for ER to form a stable complex; it has been widely used in treating BC and EC in clinical settings due to its ability to suppress cancer cell growth [5,19]. Studies have found that HOXB13 could suppress the formation of Tamoxifen–ER complex by directly inhibiting ER expression, which results in the resistance of cancer cells to Tamoxifen [129,130]. Therefore, HOXB13 could be used as a biomarker to predict Tamoxifen resistance in treating endocrine cancers (such as ER-positive BC and ER-positive ovarian cancer) [131,132] (Fig. 5A-⑦). Furthermore, HOXB13 could increase the expression of *ABCG1*, *EZH2*, and *Slug* participating in the regulation of cancer metastasis and drug resistance by directly binding to their promoters; this phenomenon leads to the resistance of lung cancer cells to cisplatin (a type of chemotherapeutic drug) and increasing the potential risk of cancer metastasis after chemotherapy [7] (Fig. 5A-⑧).

The BC index (BCI), which is determined by the ratio of *HOXB13* and *IL17B*, could be used to accurately predict the long-term recurrence of ER-positive BC patients who have previously received endocrine therapy. The BCI provides important instructions on optimizing endocrine strategies to achieve the best curative effects [130,133–135]. High levels of *HOXB13* and low levels of *IL17B* indicate that BC patients are resistant to tamoxifen therapy, which necessitates a change in treatment strategies. Some multicenter clinical trials have shown that high BCI patients receiving Tamoxifen for 5 years with an additional 5 years of letrozole or Tamoxifen adjuvant endocrine therapy could reduce the relative risk of cancer recurrence by 58% to 66%. The BCI index has been recommended as a level 1B classification for a clinically predictive biomarker of extended endocrine therapy for BC [136,137]. In addition, Goetz *et al*. [138] reported that ER-positive BC patients with higher BCI and lower cytochrome P450 2D6 (CYP2D6) could benefit more from Tamoxifen. Therefore, markers determined by CYP2D6 and BCI could provide reliable information for predicting Tamoxifen resistance in BC patients (Fig. 5A-⑨). Currently, some primary quantitative analysis index diagnostic systems have been established based on HOXB13 in the field of BC. These diagnostic systems might be a promising nano-platform for cancer therapy and cancer diagnosis.

HOXB13 as a target for clinical therapy

HOXB13 shows differential expression in human carcinomatous tissues, while its expression is low or even absent in most normal tissues. Therefore, HOXB13 may be a potential biomarker for the treatment of some cancers, and it is an effective way to control the expression of HOXB13 for preventing carcinogenesis [139,140].

Four anticancer agents have been found to suppress cancer progression through regulating HOXB13 [141]. The HDAC4 inhibitor sodium butyrate could suppress PCa progression by inhibiting the recruitment of HDAC4 to the YY1 binding site on the *HOXB13* promoter and stimulating H3 and H4 acetylation [30] (Fig. 5B-①). All-trans retinoic acid could suppress the recruitment of DNMT3b to the *HOXB13* promoter by reducing EZH2 expression, which decreases H3K27me3 and finally leads to the suppression of PCa progression [24] (Fig. 5B-②). The JQ1, which is a prototype BET inhibitor that induces G1/S inhibition and prevents transcriptional export, could disturb the localization of BRD4 to the *HOXB13* promoter and then suppress PCa progression [29] (Fig. 5B-③). The DNMT inhibitor SGI-1027 could increase *HOXB13* expression by inhibiting ~4.5 kb CpG island methylation of *HOXB13*, which in turn suppresses PCC proliferation [18] (Fig. 5B-④). Two anticancer agents could repress cancer progression through regulating the interaction between HOXB13 and other factors. One is the chromatin remodeling protein (CHD1). It acts as a cancer suppressor to inhibit the expression of AR target genes by preventing the binding of AR to HOXB13, which disturbs PCa proliferation [1,35] (Fig. 5B-⑤). The other is the RTK inhibitor Decorin, which could inhibit

PCa progression by blocking the interaction between MEIS1 and HOXB13 [52] (Fig. 5B-⑥). Moreover, two anticancer agents play roles in repressing cancer progression through regulating the downstream of HOXB13. Colchicine, which is a tubulin inhibitor, could increase *HSPB8* expression by inhibiting HOXB13 expression, which results in the repression of PCa metastasis [119] (Fig. 5B-⑦). ICG-001 could destroy the function of HOXB13 on activating target genes by disrupting WNT signaling in the process of EC metastasis [43] (Fig. 5B-⑧). Overall, HOXB13 has attracted increasing attention as a potential target for cancer therapy [142]. Controlling HOXB13 expression or its targets may be a potential strategy to repress cancer progression and decrease the number of cancer-related deaths. Additional studies should be performed to evaluate its feasibility in clinical settings.

Conclusions

In recent years, precision medicine in cancer treatment has shown remarkable vitality in clinical treatment, and HOXB13-targeted therapeutic approaches are expected to become a new focal point in cancer gene therapy research. Studies related to cancer development have progressed rapidly, with many emphasizing the importance of HOXB13 in cancer diagnosis and targeted therapy. Given the complex signal regulatory network of HOXB13 *in vivo*, combined treatment with HOXB13 inhibitors and other anticancer agents should be tailored to different cancer microenvironments for optimal efficacy. A more in-depth analysis of *HOXB13* variants and their geographic distribution characteristics may yield novel markers and anticancer strategies. These approaches could complement existing standards of care, with the ultimate goal of improving the prognosis and survival qualities of patients. Overall, with advancements in high-throughput technologies and nanotechnologies, the latest discoveries in the molecular biology of HOXB13 are expected to be applied in clinical settings.

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Compliance with ethics guidelines

Conflict of interests Jian Zhang, Ying Ju Li, Bo Peng, Xuna Yang, Miao Chen, Yongxing Li, Hengbin Gao, Haitao Li, and Ji Zheng declare that they have no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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