Homeobox Genes in Cancers: From Carcinogenesis to Recent Therapeutic Intervention

Yangyang Feng1,2, Tongyue Zhang1,2, Yijun Wang1,2, Meng Xie1,2, Xiaoyu Ji1,2, Xiangyuan Luo1,2, Wenjie Huang2,3* and Limin Xia1,2*

1 Department of Gastroenterology, Institute of Liver and Gastrointestinal Diseases, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, 2 Hubei Key Laboratory of Hepato-Pancreato-Biliary Diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, 3 Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

The homeobox (HOX) genes encoding an evolutionarily highly conserved family of homeodomain-containing transcriptional factors are essential for embryogenesis and tumorigenesis. HOX genes are involved in cell identity determination during early embryonic development and postnatal processes. The deregulation of HOX genes is closely associated with numerous human malignancies, highlighting the indispensable involvement in mortal cancer development. Since most HOX genes behave as oncogenes or tumor suppressors in human cancer, a better comprehension of their upstream regulators and downstream targets contributes to elucidating the function of HOX genes in cancer development. In addition, targeting HOX genes may imply therapeutic potential. Recently, novel therapies such as monoclonal antibodies targeting tyrosine receptor kinases, small molecular chemical inhibitors, and small interfering RNA strategies, are difficult to implement for targeting transcriptional factors on account of the dual function and pleiotropic nature of HOX genes-related molecular networks. This paper summarizes the current state of knowledge on the roles of HOX genes in human cancer and emphasizes the emerging importance of HOX genes as potential therapeutic targets to overcome the limitations of present cancer therapy.

Keywords: homeobox genes, transcription factors, therapy, biomarker, cancer progression

Abbreviation: NSCLC, non-small-cell lung carcinoma; CRC, colorectal cancer; PTC, papillary thyroid cancer; LSCC, laryngeal squamous cell cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; FASN, fatty acid synthase; LUAD, lung adenocarcinoma; HNSCC, head and neck squamous cell carcinoma; TNBC, triple negative breast cancer; CMM, cutaneous malignant melanoma; ESCC, esophageal squamous cell carcinoma; NPC, nasopharyngeal carcinoma; CHOL, cholangiocarcinoma.
1 INTRODUCTION

1.1 General Overview

The homeobox (HOX) genes were initially discovered in 1992 with the roles in embryogenesis in *Drosophila melanogaster*, where mutations in antennapedia and bithorax clusters were observed to lead to abnormal body development (1). These mutations lead one body segment to emerge similar to another segment and is originally called the term "homeotic" mutations since the 1990s (2).

The HOX genes encode a family of transcription factors that regulate embryogenesis and morphogenesis during the embryonic period and adulthood. These genes are highly conserved and contain homologous domains in almost all eukaryotic cells (3). The HOX genes comprise a highly conserved sequence of 180-183 base pairs encoding a homeodomain of 60 or 61 amino acids helix-turn-helix motif (2). The specific structure was initially characterized by magnetic resonance spectroscopy imaging.

In the human genome, according to the sequence similarity and position correlation in the chromosome, 39 HOX family genes can be divided into 4 clusters, namely HOXA, HOXB, HOXC, HOXD. The number after the subgroup HOXA, HOXB, HOXC, HOXD increases orderly in a 3' to 5' orientation, which is shown in Figure 1. Each cluster has between 9 and 11 genes in a row on a homologous strand of DNA, which contains duplication and divergence of ancestral HOX genes.

1.2 Physiological Function of HOX Genes

HOX genes encode a family of master transcriptional regulators throughout growth and development in human tissues and organs. This period monitoring elicits distinct and temporospatial limb and organ developmental programs along the anterior-posterior axis (99). Researchers found the chromosomal arrangement of HOX genes was closely related to their localization order of genetic expression (100).

Plenty of scientific evidence suggests that the specific functions of individual HOX genes largely reflect their regional and restricted expression patterns. The disruption of the chromosome region related expression pattern may lead to developmental defects and diseases, especially human cancer (101).

HOX proteins encoded by HOX genes are key components of substantial metabolic processes such as lipid metabolism, and their...

![FIGURE 1](https://example.com/figure1.png)

**FIGURE 1** | Overview of HOX involvement in different tumors in human. The colors of HOX molecules indicate regulations in relevant tumor cell. The red font means the corresponding HOX genes is up-regulated in tumor, while the blue font means the corresponding HOX genes is down-regulated in comparison. Regulation of HOX factors in various tumor types described in this figure legend. [brain cancer mainly includes the glioma and neuroblastoma (4–11), lung cancer (12–24), hepatocellular carcinoma (25–31), bladder cancer (32, 33), cholangiocarcinoma (34), head and neck squamous cell carcinoma (35, 36), breast cancer (21–23, 37–39), gastric carcinoma and esophagus cancer (55–64), prostate cancer and renal carcinoma (43, 65–72), ovarian cancer (73–79), endometrial cancer and cervical cancer (80–84), leukemia (85–98), skin carcinoma (99–100).]
roles in organogenesis and tumorigenesis have been studied in detail over the past decade (12, 37, 73, 102–105). Pluripotent embryonic carcinoma cells have been associated with the differentiation of a broad spectrum of tissues early in development in mice embryos (106). This process appears to be related to retinoic acid reactions, the chromosomal region determining the aforementioned relation was regulated by HOX gene (96, 107).

In conclusion, HOX genes act as primary regulators to regulate downstream target molecules (103). HOX genes play an essential role in embryonic development, including morphogenesis, organogenesis, and differentiation of a variety of tissues and organs (108).

2 DEREGULATION OF HOX GENES IN HUMAN CANCER

Over the past several decades, we have come to understand that a great many genes and proteins controlling embryogenesis usually partake indispensable effects in carcinogenesis likewise. Many genes identified as pivotal genes in carcinogenesis, for example, oncogenes or tumor suppressor genes, have been discovered to play primary roles in embryogenesis correspondingly. It indicates both processes are tightly linked (109). The familiar components of signal transduction pathways, such as the Sonic Hedgehog pathway, Wingless-Type MMTV Integration Site Family, Notch pathway, Paxillin pathway, and Sry-box transcription factors family members, closely act in accordance with the above rules.

This close relationship between embryogenesis and carcinogenesis supports the lineage-dependency theory. The theory proposes that the cellular mechanisms participating in lineage heredity and adaptability during development, potentially underlies tumorigenic mechanisms in humans (110). The HOX genes might be applicable to the lineage-dependency theory. Apart from the indispensable involvement of HOX genes in embryonic development in physiological status, their abnormal expression, has long been linked to tumors. Initially, these genes were thought to be related to human cancers in the hematologic system and embryo. Later, many other kinds of tumors were also noticed to be associated with deregulated HOX genes (85, 101, 111). In the context of cancer development, the abnormal expression of HOX gene may affect cell proliferation, differentiation, apoptosis, motility, angiogenesis, autophagy, and cell receptor signaling (112). HOX genes in the hallmarks of cancer are shown in Figure 2.

The protein products of HOX genes are initially thought to be transcription factors that accelerate cancerization since HOX proteins are deregulated in carcinogenesis. In the above process, HOX proteins govern the intricate balance of multiple signaling pathways on and off, and affect downstream targets of these pathways (113), so as to determine different cancer outcomes.

Subsequent studies have shown that HOX genes act not only as transcriptional activators but also as transcriptional repressors in cancer. This abnormal regulation of HOX genes in cancer suggests that HOX genes expression is an integral part of the regulatory network (103, 114, 115).

HOX genes in tumor show temporospatial deregulation pattern, different from that in normal tissues and organs. Besides, the gene dominance in expression level, that is, the aberrantly increased expression level of HOX genes in specific tissue types, the mechanism is also proposed to explain HOX genes relevant to cancer. The targets identified for HOX factors in human cancer are shown in Table 1 (4–7, 13–20, 25–30, 32–35, 38–49, 55–62, 65–70, 74–76, 80–83, 86–91, 116–121, 127–130, 133–149).

2.1 Direct Role: As Oncogenes

The HOX genes have been reported to act as oncogenes and contribute to tumor progression in several types of cancer. For example, simultaneous overexpression of HOXA9 and MEIS1A induces acute myeloid leukemia in rats (92, 131). In breast cancer, HOXB7 has been reported as an oncogene because its upregulation appears to promote the expression of bFGF and induce the epithelial-mesenchymal transitions (EMT) (15, 27, 34). In colorectal cancer, HOXB5 overexpression mediated by CXC chemokine ligand 12 facilitates metastasis through transactivating downstream protein CXCR4 and ITGB3 (134). HOXB13 seems to be an oncogene for ovarian and prostate cancer. Its knockout in ovarian cancer cells results in reduced tumor invasion (45, 65, 71, 138, 141). On the contrary, its ectopic expression promotes cell proliferation and nonanchoring. Mutations and growing resistance to tamoxifen-mediated apoptosis in the cell tumor antigens P53, Myc, and Ras are included in mouse ovarian cancer cells (43–46). In addition, HOXB13 overexpression appears to promote invasion of these types of cancers. In prostate cancer, HOXB13 regulates the prostate-derived ETS family members and also facilitates cell invasion (140). As HOXB3 in glioblastoma, its knockout leads to cancer cell suppression (150). In squamous carcinoma of the cervix, HOXC10, which is overexpressed and thought to be an oncogene, is knocked out to reduce invasiveness (6, 19, 29, 61). In colorectal cancer, HOXA13 overexpression mediated by insulin-like growth factor 1 promotes metastasis through upregulating downstream targets ATP-citrate lyase and insulin-like growth factor 1 receptor (133). Ectopic overexpression of ATP-citrate lyase and insulin-like growth factor 1 receptor rescues the decreased colorectal cancer metastasis induced by HOXA13 knockdown (133). HOXC10 overexpression mediated by Interleukin 1β facilitates hepatocellular carcinoma (HCC) metastasis (29). The above studies implicate HOX genes as oncogenes and prognostic biomarkers. Hence, targeting HOX genes’ relevant pathways is likely to be the promising therapeutic option for clinical cancer prevention (29).

2.2 Direct Role: As Tumor-Suppressor Genes

Basing on our review of the literature, we found the expression of specific HOX genes in cancers tends to vary with tissue type and tumor sites. Besides, the HOX genes have been found to behave as tumor-suppressor genes and dedicate to tumor suppression in several cancers.
HOXC8 in nasopharyngeal cancer is silent and its ectopic expression causes the inhibition of tumor growth (143). In vitro and in vivo, in addition, HOXA5 is often down-regulated in breast cancer and appears to mediate apoptosis through p53 or caspases 2 and 8 in normal cells, thus having a tumor-like effect inhibition (50, 121, 122). Downregulation of HOXC9 in infant neuroblastoma appears to lead to increased cancer cell survival and tumor growth (5). HOXB1 is also significantly down-regulated in glioma cells, its knockdown promotes proliferation and invasion, inhibits apoptosis of cancer cells in vitro, and leads to poor survival (5, 8, 151).

The expression changes of HOXA4, HOXA9, and HOXD10 cause abnormal proliferation and differentiation of colorectal carcinoma cells and contribute to tumor development (14, 74, 87, 127). In addition, HOXB3 overexpression promotes the proliferation and invasion of glioblastoma cells, acute myeloid leukemia, pancreas, prostate, ovarian, and lung cancer (74, 93, 150, 152, 153). Excessive HOXB7 inducing MET in breast cancer cells also interferes with DNA repair and tamoxifen (136). HOXA5 down-regulation is discovered in multiple tumors, including liposarcoma, cervical cancer, breast cancer, which suggests that HOXA5 may be an important tumor suppressor (21, 51, 84, 123). The promoter methylation and downregulation of HOXA5 during the epigenetic deregulation decrease RARβ-driven apoptosis mediated by caspase 2 and caspase 8. Therefore, HOXA5 consumption in breast cells causes a lack of epithelial cell characteristics as well as an increase of stem cell property and cellular plasticity, eventually leads to a more aggressive phenotype (119).

Therefore, the abnormal expression of the HOX genes in various cancers seems to indicate that random alterations are not necessary for the health maintenance and survival of cancer cells. Instead, abnormal expression of specific HOX genes in cancer seems to play a large part in the development of cancer.

However, HOX genes may show a predisposition. It is up-regulated or down-regulated in certain tumors, promoting cancer progression or inhibition in certain cases. Thus, they can be regarded as oncogenes or tumor suppressor genes, usually depending on the corresponding tumor microenvironment.
### 2.3 Indirect Role: Epigenetic Control via HOX Genes

HOX proteins are also involved in chromatin posttranslational modifications, epigenetically affect the expression of crucial cancer progression genes. For example, HOXB3 regulates the expression of DNA methyltransferase, which seems to be of considerable relevance to understanding the mechanisms involved in tumorigenesis.

In fact, all cancer progression has common abnormalities, such as the massive epigenetic silencing of tumor suppressor genes. The mechanisms behind this phenomenon are remained to be fully understood. The DNA methyltransferase protein family consists of DNA methyltransferase (DNMT)-1, DNMT3A, DNMT3B, and DNMT3L (154). The last is associated with de novo methylation of DNMT3A/B, which is required during embryonic development, imprinting, and X chromosome inactivation. DNMT1 maintains the DNA methylation profile of the genome during each cell cycle, while DNMT3a and DNMT3b are involved in de novo DNA methylation. DNMT1 is also associated with the establishment of DNA methylation in the methylated state.

| TABLE 1 | Targets identified for HOX factors in human cancer. |
|---------|--------------------------------------------------|
| **HOX protein** | **Role** | **Interference** | **Cancer type** | **Year** | **Reference** |
| HOXA1 | Oncogene | Sequester G9a/EZH2/Dnmts, sponge miR-193a-5p, via cyclin D1, via miR-100 | Breast cancer, glioma, GC, lung cancer | 2014, 2016, 2018 | (38, 63, 97, 116) |
| HOXA3 | Oncogene | Upregulate methylation level, promote differentiation to angiogenesis, confer cisplatin resistance | NSCLC, PTC, blood | 2011, 2019 | (13, 117, 118) |
| HOXA4 | Tumor suppressor | Downregulate β-catenin, Cyclin D1, c-Myc and survivin, inhibit activation of Wnt signaling, upregulate GSK3β | Lung cancer, ovarian carcinoma | 2009, 2018 | (14, 74, 79) |
| HOXA5 | Tumor suppressor | Induce apoptosis mechanism mediated by casp2 and casp8, regulate E-cadherin and CD24, methylate promoter region & limit p53 expression | Breast cancer, mammary cancer, cervical cancer | 2015-2021 | (9, 21, 39-41, 50, 51, 80, 84, 119-128) |
| HOXA6 | Oncogene | Coexpress with PBX2 | GC, CRC, leukemia | 2021 | (55) |
| HOXA7 | Oncogene | Combine to Snail promoter, cyclin E1/CDK2, activate Snail | Cervical cancer, HCC | 2016, 2020 | (25, 81) |
| HOXA9 | Oncogene | Pioneer factor at de novo HOXA7 promoter, cyclin E1/CDK2, activate Snail | Cervical cancer, HCC | 2016, 2020 | (25, 81) |
| HOAX10 | Oncogene | Suppress FASN transcription by forming a protein complex with AR and prevent AR recruitment to FASN gene promoter, hinder mir195 | Prostate cancer, testicular cancer | 2020 | (39) |
| HOAX11 | Oncogene | LncRNA HOXA11-AS recruit EZH2 along with the histone demethylase LSD1 or DNMT1 | GC, LUAD, renal cancer | 2016, 2017, 2018 | (56, 57) |
| HOAX13 | Oncogene | IGF-1 | CRC, GC | 2021 | (133) |
| HOAX4 | Tumor suppressor | Downregulate activity of Wnt/β-catenin signaling pathway, downregulate P-gp, MRP1 and BCRP expression | Cervical cancer, leukemia | 2016, 2021 | (82, 91) |
| HOAX5 | Oncogene | Transactivate CXCR4, ITGB3, FGFR4, CXCL1 | HCC, CRC, breast cancer, HNSCC, GC | 2015, 2021 | (26, 42, 134) |
| HOAX7 | Oncogene | Reprogram to iPSC with comparable efficiency to LIN28B or c-MYC, activate TFGR3 signaling pathway | HCC, CRC, breast cancer, HNSCC, GC | 2016, 2018 | (15, 27, 34, 58, 135, 136) |
| HOAX8 | Oncogene | Instigate BACH1-mediated transcriptional cascade, via ZEB2 targets | Lung cancer, GC | 2017, 2020 | (59, 137) |
| HOAX13 | Tumor suppressor | Downregulate activity of Wnt/β-catenin signaling pathway, downregulate P-gp, MRP1 and BCRP expression | Colon cancer, lung cancer, prostate cancer | 2015-2019 | (16, 43-46, 60, 65-68, 138-141) |
| HOAX6 | Prognosis marker, oncogene suppressor | Enhance BCL2-mediated antiapoptotic effects, drive MET | Prostate cancer, cervical cancer, HCC | 2019 | (28, 69, 83) |
| HOAX8 | Oncogene | Upregulate TGFβ1, repress LMP1 | NSCLC, TNBC | 2018 | (17, 47, 48, 142, 143) |
| HOAX9 | Oncogene | Mediate autophagy, via mir-495/HOXC9 axis, promote multi-chemosensitivity | Bladder cancer, neuroblastoma, NSCLC | 2011, 2015, 2016 | (4, 5, 32) |
| HOAX10 | Oncogene | Via upregulating PDK1, VASP, EMT, promote angiogenesis, induce immunosuppressive gene | HCC, lung cancer, ovarian cancer | 2014-2020 | (6, 7, 19, 29, 49, 61, 144, 145) |
| HOAX13 | Oncogene | Modulate CCND1 & CCNE1 | Lung adenocarcinoma | 2017 | (23) |
| HOAX13 | Tumor suppressor | Inhibit HDAC1 via ITGA2 pathway & MAPK/ AKT signaling | HCC, CRC | 2019, 2020 | (146, 147) |
| HOAX13 | Oncogene | Enhance LINC01116 contribution to progression of BCa via targeting ELK3 & HOXD8 | Bladder cancer | 2020 | (33) |
| HOAX9 | Oncogene | Transactivate RUFY3 & ZEB1, promote MET | GC, HCC | 2015, 2019 | (30, 62) |
| HOAX10 | Tumor suppressor | Inhibit RHO/AKT/MAPK pathway, upregulate mir-10b | CRC | 2019 | (76, 148) |
| HOAX13 | Tumor suppressor | Inhibit SMAD1, suppress BMP4 | Prostate cancer | 2021 | (70) |
division. DNMT3A and DNMT3B can actively add de novo methyl to DNA sequences to control gene expression and play a key role in cancer progression.

Palakurthy has shown that DNMT3B is the target of HOXB3 protein and is involved in the epigenetic regulation of tumor suppressor gene RASSF1A in lung adenocarcinoma and other cancers (153). HOXB3 also directly interacts with DNMT3B to promote the occurrence of leukemia in acute myeloid leukemia.

In addition, HOX genes may also play a role in post-translational modification of chromatin and affect gene expression. For instance, Heinonen has shown that HOXB7 can directly bind to chromodomain protein Y-like and enhance the histone methyltransferase activity of Polycomb Complex 2 and induce gene silencing as typical for trimethylate lysine 27 of histone H3 (155).

2.4 Tumor Proliferation, Invasion, and Metastasis

Proliferation phenotype has been found in various HOX-related researches, especially in leukemia, where HOX upregulated expression is often resulted from translocation mutations or altered regulation in the trithorax homologue myeloid-lymphoid leukemia (112). Invasion and metastasis phenotypes caused by abnormal HOX gene expression have been mostly studied in solid tumors, where HOX gene deregulation is usually due to loss-of-function mutations or gain-of-function mutations, or undefined mutations in upstream regulators.

In recent work, HOXC13 promotes cell proliferation by modulating the expression of cyclin D1 and cyclin E1 in lung adenocarcinoma. HOXA5 inhibits cell proliferation by regulating p53 expression in liposarcomas and p21 in non-small lung cancers (20, 63, 84, 120). Although HOXB13 overexpression promotes prostate cancer metastasis by downregulating intracellular zinc and upregulating NF-kappaB signaling pathways, HOXB13 consumption promotes proliferation of PC-3 and LNCaP cells by controlling G1/S and G2/M checkpoints (16, 60, 67, 138, 141).

HOX proteins affect cell cycle process by regulating cell cycle-related proteins (156), thus also affect proliferation and apoptosis in cancer progression. Growing evidence is noticeable that many HOX transcription factors are abnormally expressed in cancer, and their dysregulation significantly promotes tumor invasion and metastasis.

HOXD9 interacts with the promoter region of zinc-finger E-box binding homeobox (ZEB)-1, inhibition of ZEB1 induced by HOXD9 suppresses HCC cell migration, invasion as well as EMT (30). In addition, according to microarray analysis, ZEB2 may be a downstream cofactor of HOXB8 (59). Patients enrolled in studies have shown that high HOXB13 expression promotes the progression of lung adenocarcinoma and predicts poor prognosis (16).

In epithelial ovarian cancer cells, HOXA9 not only promotes the growth of epithelial ovarian cancer cells in vivo by activating transcriptional activity of the gene encoding transforming growth factor β (TGFβ)-2, but also binds to the promoter of the cadherin3 gene that encodes P-cadherin to induce intraperitoneal dissemination (77, 94). Many reports suggest the temporospatial deregulation of HOXA9 is associated with primary tumors and specific histological subtypes. HOXA9 is of therapeutic potency, while the potency is limited by the low membrane permeability.

2.5 Angiogenesis

Angiogenesis is an important link during tumor progression. HOX proteins affect angiogenesis mainly by regulating VEGF expression (7). For example, HOXC10 level is statistically correlated with VEGFA expression in gliomas. HOXC10 upregulates VEGFA expression transcriptionally by binding to its promoter, and the post-translational modification of histones mediated by protein arginine methyltransferase 5 and WD repeat domain 5 is required in angiogenesis (7). MiR-203a negatively targets HOXD3 directly by targeting the VEGFR promoter region and increases VEGFR expression.

HOX protein expression also plays an important role in endothelial cells (EC) (146). For instance, HOXA5 is expressed in static EC but not in activated angiogenic EC. HOX A5 continuously increases the TSP-2 expression and decreases the VEGF expression, thereby inhibiting histopathological angiogenesis (124, 125). In addition, HOX A5 is absent in EC of proliferative hemangioma (9). HOX A5 increases the mRNA and protein expression of Akt1, further enhances Akt activity by coordinating the down-regulation of PTEN, thereby increasing the stability of the capsular patellar junction (126).

2.6 Resistance in Anti-Cancer Drugs

HOX proteins are involved in resistance to the anti-cancer drugs in cancers, especially in myeloid leukemia, HCC, breast cancer, and lung cancer. HOX proteins regulate various non-coding RNAs (ncRNAs) which influence cancer cells chemotherapy resistance. In particular, we take the example of the role of HOXB13 in mediating chemotherapy resistance in lung adenocarcinoma. HOXB13 upregulates a series of drug-transfer and drug-resistance-related genes by directly binding to their promoters and forming the cisplatin-HOXB13-ABCG1/EZH2/Slug network, including ATP Binding Cassette Subfamily G Member 1, Enhancer Of Zeste 2 Polycomb Repressive Complex 2, and Slug (16, 139). Levels of HOXB13 and its target genes may help predict sensitivity of platinum-based chemotherapy in lung adenocarcinoma patients (16).

2.7 HOX-Mediated Molecular Crosstalk During Tumorigenesis

2.7.1 Post-Translational Modifications

A variety of signaling pathways that regulate proliferation, apoptosis, differentiation, movement, and angiogenesis, interact with HOX transcription factors family. Post-translational modifications of HOX protein also play a key role in tumorigenesis. HOX post-translational modifications are an under-valued project. In most eukaryotic proteins, the turn-over, intracellular localization, molecular interactions and activity are modulated by post-translational modifications. The post-translational modifications of HOX proteins in cancer mainly
contributes to the modulation of protein stability, DNA binding, transcriptional activator-like effectors interaction, transcriptional activation capacity, unidentified cellular impact (157).

2.7.2 MicroRNA and Non-Coding RNA
Of the 39 HOX genes, 30 HOX genes contain more than one conserved nucleotide sequences that are expected to be targets of miRNAs in vertebrate (2). We found that the HOX targeting genes are mainly located on the 3’ side of each HOX miRNA site. This study shows that HOX miRNAs help inhibiting abundant pre-gene expression, hence enhancing the prevalence of post-genes. In patients with gastrointestinal stromal tumors, the level of miRNA196a is positively related to higher tumor histologic grade, higher recurrence rate, and lower survival rate (64).

In addition, HOX transcribed antisense RNA (HOTAIR) also contributes to HOX expression regulation. HOTAIR is a 2.2-kilobase long non-coding RNA that is transcribed from the antisense strand of HOXC clusters, and its function is to inhibit the transcription of 40 kilobases of HOXD clusters (158, 159). The mechanism of action of these long non-coding RNAs has not been fully determined. However, HOTAIR has been shown to regulate chromatin state and kinetics by binding to specific chromatin modification complexes. The trimethylation of histone H3 lysine 27 at the HOXD site requires HOTAIR/PRC2 interactions. Knocking out HOTAIR activates HOXD gene transcriptional activity on human chromosome 2 (158, 160, 161). Thus, it is possible to modulate the HOXD gene by modulating HOTAIR levels, which has implications in cancer therapy. For example, the expression of HOTAIR is closely related to the neoplasm staging and poor prognosis of glioma. Reducing HOTAIR expression induces inhibition of colony formation, G0/G1 cell cycle arrest, and inhibition of tumor growth in situ (10). Thus, HOTAIR seems to serve as a prognostic factor for survival, as well as a biomarker for identifying molecular subtypes in cancer (162).

Recent evidence underscored the function of long noncoding RNAs (lncRNAs)-driven hepatocarcinogenesis. The expression level of lncRNA HOXA transcript at the distal tip (HOTTIP) and HOXA13 is associated with metastasis and survival in HCC patients. It indicates the prospective potency of HOTTIP and HOXA13 to be the predictive biomarker in HCC (163).

Summing up the above, we highlight the specific roles of miRNAs and lncRNAs in human cancer. They perform not only as the intermediary between DNA and protein, including chromosome remodeling, transcription, and post-transcriptional processing, but as leading characters in body balance adjustment during congenic malformation, oncogenesis, metabolic processes, and deregulation of cell cycle (164).

3 HOX TRANSCRIPTION FACTORS AS THERAPEUTIC TARGETS

3.1 HOX Genes Act as a Key Intermediate Point in the Anti-Cancer Progression
HOX proteins interact with specific cofactors to select their downstream binding sites in the genome. In vertebrates, those including pre-B cell leukemia transcription factor (PBX) and mouse heterotopic cell cycle family of homologous domain protein. In addition, these HOX cofactors can increase the nuclear translocation of HOX protein from the cytoplasm to the nucleus. Nuclear translocation of HOX protein is inhibited by suppressing the formation of HOX/PBX dimer, which impairs the function of HOX transcript factors (165). Therefore, considering the use of HOX protein as cancer therapeutic targets, its interaction with cofactors needs to be determined. Therapeutic values of HOX factors in human cancer are seen in Table 2 (4, 7, 13, 14, 17, 18, 22, 23, 25–27, 29, 31, 32, 35, 41, 45, 56, 57, 68, 71, 72, 81, 82, 84, 87, 88, 90, 97, 116, 117, 127, 128, 132–135, 137, 141, 147, 148, 153, 166, 167).

Morgan et al. have found HXR9 peptides specifically target the interaction between HOX and PBX (78, 168). HXR9 inhibits HOX function by preventing its binding to PBX, which leads to apoptosis in multiple mouse breast cancer derived cell lines (168). In addition, the interaction between HOX and HXR9 has been shown to cause apoptosis in numerous cancers, including melanoma, mesothelioma, myeloma, renal cancer, prostate cancer, lung cancer, ovarian cancer, pancreatic cancer, squamous cell cancer of the head and neck, and oral cancer (58, 78, 95, 98, 168). Kaspar and Reichert have already used HOX/HXR9-based treatments in cancer treatments, and Morgan and others are exploring a variant of HXR9 for intratumoral injection in clinical trials (168). The HOX gene targeting therapy is also being explored through RNA interference approaches (158). For example, MicroRNAs transcribed in HOX clusters, namely miR10A32 and miR196B33, regulate HOX expression through RNA interference (158). These miRNAs cleave or inhibit the translation of HOX mRNA. The use of these miRNAs in cancer cells in vitro seems to modulate HOX gene expression and its effect on cancer progression.

In fact, HOTAIR has the potential to be an effective therapeutic target for many types of cancer, where abnormal HOX expression has been found to be associated with cancer progresses, such as cancers in breast, stomach, colon, cervix, lung, and liver (11, 12, 24, 36, 52–54, 158, 159, 169, 170). For example, HOTAIR is highly expressed in cervical cancer compared to normal cells (158, 159, 169). However, its knockout in cervical carcinoma cells induces apoptosis and inhibits tumor proliferation, migration, and invasion.

3.2 HOX Genes as Therapeutic Targets
Previous studies have shown that HOX protein exerts carcinogenic activity not only through its reversed transcription ability but through its protein interaction network.

When designing domain-specific HOX inhibitors, gene targeting must be taken into account. The problem in bringing monoclonal antibodies into clinical therapies is their nuclear localization. To address the above issue, the focus of next-generation immunotherapies is to develop smaller monoclonal antibody fragments or totally new entities to improve tissue permeability and subcellular localization. These crucial immunotherapeutic strategies are also focused on addressing the treatment of hematologic tumors and solid tumors.

Since HOX protein is closely linked to brain malignancies where the blood brain barrier is a major challenge for drug
| Gene      | Down regulation effects                                                                 | Downstream regulated molecules or pathways          | Upstream regulatory molecules | Tumor x cell lines x normal tissues | Related targeting molecules | Intervention therapy | Clinical trial number & Reference |
|-----------|----------------------------------------------------------------------------------------|---------------------------------------------------|-------------------------------|-----------------------------------|-----------------------------|-----------------------|-------------------------------|
| HOXA1     | Proliferation, migration, invasion, metastasis                                          | Wiping out epigenetic silencing of HOXA1          | HOTAIRM, G9a, EZH2            | GBM                              | Histone modification of H3K9, H3K27 | /                     | (116)                         |
| HOXA1     | Metastasis, invasion                                                                     | MITF                                             | TGF-β, Mir-100, Melanoma       | TGF-β signaling                  | HOXA1                       | /                     | (97)                          |
| HOXA1     | Occurrence, development                                                                  | Chemoresistance                                  | HOXA-AS2, miR-15a-5p, PTCC     | HOXA-AS2/miR-15a-5p/             | HOXA3 axis                  | /                     | (118)                         |
| HOXA3     | Chemoresistance                                                                        | EMT& Cisplatin resistance                        | HOXA-A3, NSCLC                | HOXA-A3                          | /                           | /                     | (13)                          |
| HOXA4     | Growth, migration, invasion                                                              | β-catenin, cyclin D1, c-Myc, survivin             | GSK3β                         | Lung cancer                      | GSK3β/LiCl                  |                     | (14)                          |
| HOXA5     | Angiogenesis                                                                            | MIR-130-3p, Exosomal miR-181d-5p                  | HCC                           | Breast cancer                     | SP1 inhibitor               |                     | (23)                          |
| HOXA5     | Growth, migration, invasion                                                              | CAF                                              | HOXA9/MiR-146a                 | Histone H3K4 methylation         | HOXA9/Meis/Jkb/feedback loop | /                     | (67)                          |
| HOXA5     | Arresting cell cycle                                                                     | TP53, P21                                        | Binding to TAAT motif within promoter of TP53 | Cervical cancer                  | Wnt/β-catenin               | /                     | (84)                          |
| HOXA7     | Migration, invasion                                                                     | Snail                                            | /                             | Cervical cancer                  | HOXA7/Snail                 | /                     | (25)                          |
| HOXA7     | Proliferation, invasion                                                                  | /                                                | /                             | /                                | /                           | /                     | (81)                          |
| HOXA9     | Leukemogenesis                                                                          | STAT5, AP1                                       | JAK3/STAT5                     | Leukemia                          | Mutant JAK/STAT/            |                     | (88)                          |
| HOXA9     | Leukemogenesis                                                                          | CEBPα, ML3, ML4, Meis, Syk                        | HOXA9/Meis                     | Leukemia                          | Histone H3K4 methylation     | /                     | (128)                         |
| HOXA9     | Leukemogenesis                                                                          | Erg                                              | Trib1                          | Leukemia                          | HOXA9/Trij1/Jkb             |                     | (91)                          |
| HOXA9     | Leukemogenesis                                                                          | HOXA9                                             | Onco-miR-365                   | CSCC                              | HOXA9-Met-365/HIF1α axis    | /                     | (127)                         |
| HOX9      | Tumor aggression                                                                        | HOXA9                                            | BRCA1                          | Breast cancer                     | /                           |                     | (132)                         |
| HOX10     | Tumor aggression                                                                        | HOXA10, CCSCs                                    | LINC00355/miR-195, EZH2       | GC                                | LINC00355                   | /                     | (35)                          |
| HOX11     | Proliferation, cell-cell adhesion pathway                                                | LncRNA HOXA11-AS, LINC00355/miR-195, EZH2       | GC                             | GC                                | LINC00355                   | /                     | (58)                          |
| HOX11     | Metastasis, invasion                                                                    | β-catenin, P21, KLF2, ACLK, IGFR1                 | WDR5/EZH2/STAU1, IGFR1         | GC                                | EZH2/ROX11-AS/              |                     | (133, NCT01154335, NCT01016860) |
| HOX11     | Metastasis                                                                             | β-catenin, P21, KLF2, ACLK, IGFR1                 | WDR5/EZH2/STAU1, IGFR1         | GC                                | EZH2/ROX11-AS/              |                     | (133, NCT01154335, NCT01016860) |
| HOX13     | Tumor aggression                                                                        | RASSFIA, DNMT3B                                  | POL2                           | Lung adenocarcinoma               | RASSFIA/epigenetic silencing | /                     | (153)                         |
| HOX13     | Tumor aggression                                                                        | CDCA3                                            | /                              | Primary prostate cancer/PC-3/    | HOXB3                       | /                     | (72)                          |
| HOX13     | Arresting cell cycle                                                                    | β-catenin, TCF, c-Myc, survivin                  | /                              | Cervical cancer                   | Wnt/β-catenin               | /                     | (82)                          |
| HOX15     | Metastasis                                                                             | ITGB3, CXCR4                                    | CXCL12                          | CRC                               | CXC4/AMD3100                | /                     | (134, NCT02179970)           |
| HOX15     | Metastasis                                                                             | CXCL1, FGFR4                                    | FGFR1                           | HCC                               | FGFR4/BLU-554               | /                     | (26, NCT02508467, CTO4194801) |
| HOX15     | Metastasis                                                                             | TGFβ2, SMADS                                    | /                              | Breast cancer                     | MET                          | /                     | (135)                         |
| HOX15     | Metastasis                                                                             | c-Myc, Slug                                     | /                              | HCC                               | MET                          | /                     | (27)                          |
| HOX15     | Invasiveness                                                                           | BACH1                                            | /                              | CRC                               | /                           | /                     | (137)                         |
| HOX15     | Angiogenesis                                                                           | IL-6, VEGF                                      | /                              | Colorectal cancer                 | VEGF/Bevacizumab            | /                     | (166)                         |
| HOX15     | Migration, tumor growth                                                                 | JMUD6                                            | Ack27                           | Lung adenocarcinoma               | Ack27/VEGFr/                | /                     | (23)                          |
| HOX15     | Migration, tumor growth                                                                 | EZH2                                            | Ack27/VEGFr/                    | Clone cancer                      | Ack27/VEGFr/                | /                     | (167)                         |
| HOX13     | Tumor aggression                                                                        | /                                               | /                              | Prostate cancer                   | HOXB13, G84E variant        | /                     | (71)                          |
| HOX13     | Metastasis                                                                             | RXF6                                            | Rs339331 at 6p22               | Prostate cancer                   | RXF6                         | /                     | (68)                          |

(Continued)
TABLE 2 | Continued

| Gene      | Downstream regulated molecules or pathways | Downstream regulated molecules | Upstream regulatory molecules | Tumor x cell lines x normal tissues | Related targeting molecules | Intervention therapy | Clinical trial number & Reference |
|-----------|------------------------------------------|-------------------------------|-------------------------------|-----------------------------------|-----------------------------|-----------------------|-------------------------------|
| HOXB13    | Tamoxifen resistance of breast cancer     | IL-6                          | HBXIR                         | Breast cancer                     | HBXIR                       | Aspirin               | (45)                          |
| HOXB13    | Tumor aggression                          | β-catenin, TCF4, c-Myc        | DNMRT3B                       | RCC                               | DNMRT3B-HOXB13-c-Myc        | /                     | (141)                         |
| HOXC8     | Cisplatin chemotherapy, anti-apoptosis    | TGFR1                         | /                             | NSCLC                             | HOXC8                       | /                     | (17)                          |
| HOXC9     | Proliferation, migration,                | DAPK1-betaC1                 | /                             | Glioblastoma                      | HOXC9/autophagy             | /                     | (4)                           |
| HOXC9     | Chemoresistance                          | SRSF2, PLAU, HiC2            | MIR-193a-3p                   | Bladder cancer                     | MIR-193a-3p/DECG9/          | /                     | (32)                          |
| HOXC10    | Aberrant expression                      | HOXC10                        | PRC2                          | NSCLC                             | Kras-mutant/DECG10          | BET/MEK inhibitor       | (18)                          |
| HOXC10    | Angiogenesis                             | VEGFA                         | /                             | Gliomas                           | HOXC10/VEGFA                | Bevacizumab            | (7)                           |
| HOXD3     | Invasion                                 | Inteigrin3                   | IL1β                          | HCC                               | HOXC10/IL1R                 | Anakinra               | (29)                          |
| HOXD10    | Invasion                                 | Snail, Slug, MMP2, MMP9, MMP14, E-cadherin | MIR-23a | Glioblastoma                      | HOXC10/IL1R                 | /                     | (147)                         |

infiltration, this provides instructive thinking of treatment. Another strategy for targeting oncogenes in cancer cells is to use small interfering RNAs (siRNAs) (171). Many studies have shown inhibition of HOX expression by siRNAs can distinctly retard tumor growth and aggressiveness. Similarly, the use of siRNA strategies may be an effective therapeutic approach for targeting HOX genes in vivo.

Although the strategy is not as progressive as small molecular chemical compound inhibitors or monoclonal antibodies, efforts have been made over the past decade to implement it in cancer treatment. At present, poor uptake of cells, side effects of packaging-related methods are major obstacles to HOX targeting clinical application. As a result, current efforts are made to address a range of novel strategies for delivering siRNAs in vivo.

The small-molecule chemical inhibitors are of anticancer potential. We highlight the recent therapies targeting HOX genes-downstream proteins especially in HCC and colorectal cancer. Overexpression of HOXB5 transactivates downstream protein expression of FGFR4 and CXCL1, hence promoting HCC metastasis. The small chemical compounds application of FGFR4 inhibitor BLU-554 and CXCR2 inhibitor S265610 sharply inhibits HCC metastasis mediated by HOXB5 (26). Integrins are also involved in HOX-induced cancer metastasis. In CAOV-3 cells, HOXA4 overexpression inhibited migration and increased the protein level of β1 integrin, suggesting that the β1 integrin may be involved in HOXA4’s inhibitory effect on cell motility (79). In HOXC10-VASP/IL-1R1 mediated HCC metastasis, daily administration of IL-1R1 antagonist anakinra dramatically prolongs survival time (29). In colorectal cancer, the molecule network IGF1-HOXA13-Acry/IGF1R and CXCL12-HOXB5-CXCL4/ITGB3, targeted blocking the downstream protein with small molecular compounds serves as a promising anticancer therapy (133, 134).

Furthermore, natural and synthetic drugs regulating HOX genes network are associated with anticancer and antibacterial activities. For instance, researchers synthesized the new molecule 5H-pyrido[3,2-a] phenozone-5-one in the laboratory, evaluated its ability to regulate the activity of IncRNA HOTAIR and HOXC locus genes from HOXC9 to HOXC13 in MCF-7 human breast cancer cell lines, and confirmed that 5H-pyrido[3,2-a] phenozone-5-one was able to inhibit the relevant HOX gene expression and counteract the pathogenesis of breast cancer (172).

The discovery of targeting downstream molecules with chemical compounds has enhanced the potential to specifically target HOX genes intermediated network and eliminate the cancer development, which may improve clinical outcomes in cancers.

4 CONCLUSION

Although it is difficult to intercept various transcription factors, alternative strategies based on the exploitation of the associated molecular networks are emerging. The HOX genes play an important role in cancer progression, showing great plasticity and interfering with many molecular mechanisms. Abnormal HOX expression by altering its homologous box methylation profile, is often associated with cancer. In addition, different HOX gene regulatory features describe different cancer types and are increasingly being used as cancer biomarkers. Their role in cancer progression is based on the ability to control gene expression either directly as transcriptional regulators or indirectly through epigenetic control. In fact, HOX proteins have been shown to be involved in different epigenetic mechanisms involved in DNA and histone methylation, which may be related to the epigenetic regulation of multiple cancer related genes. Therefore, it is very important to seek pharmacological agents that are synthetically lethal in conjunction
with HOX overexpression. Therapies targeting HOX molecules should intake the functional redundancy among the different HOX family members, so that appropriate therapeutic combination can be created. There is an urgent need for a more comprehensive understanding of their biology, and identifying their gene targets and molecular networks involved in tumor progression.

AUTHOR CONTRIBUTIONS

Conceptualization, YF, and LX. Writing—review and editing, YF, TZ, YW, MX, XJ, WH, and LX. Supervision, TZ, MX, XJ, XL, and LX. Project administration, WH and LX. Funding acquisition, WH and LX. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Mallo M, Alonso CR. The Regulation of Hox Gene Expression During Animal Development. Dev (Cambridge England) (2013) 140:3951–63. doi: 10.1242/dev.068346
2. Holland PW. Evolution of Homeobox Genes. Wiley Interdiscip Rev Dev Biol (2013) 2:31–45. doi: 10.1002/wdev.78
3. Montavon T, Soshnikova N. Hox Gene Regulation and Timing in Embryogenesis. Semin Cell Dev Biol (2014) 54:76–84. doi: 10.1016/j.semcdb.2014.06.005
4. Yuan F, Huang M, Liu W, Ding H, Yang L, Cui H. Homeobox C9 Suppresses Beclin1-Mediated Autophagy in Glioblastoma by Directly Inhibiting the Transcription of Death-Associated Protein Kinase 1. Neuro-Oncology (2016) 18:189–29. doi: 10.1093/neuonc/nov281
5. Mao L, Ding J, Zha Y, Yang L, McCarthy BA, King W, et al. HOXC9 Links Cell-Cycle Exit and Neuronal Differentiation and Is a Prognostic Marker in Neuroblastoma. Cancer Res (2011) 71:4314–24. doi: 10.1158/0008-5472.Can-11-0051
6. Li S, Zhang W, Wu C, Gao H, Yu J, Wang X, et al. HOXC10 Promotes Proliferation and Invasion and Induces Immunosuppressive Gene Expression in Glioma. FEBS J (2018) 285:2278–91. doi: 10.1111/febs.14476
7. Tan Z, Chen K, Wu W, Zhou Y, Zhu J, Wu G, et al. Overexpression of HOXC10 Promotes Angiogenesis in Human Glioma via Interaction With PRMT5 and Upregulation of VEGF Expression. Theranostics (2018) 8:5143–58. doi: 10.7150/thno.27310
8. Han L, Liu D, Li Z, Tian N, Han Z, Wang G, et al. HOXB1 Is a Tumor Suppressor Gene Regulated by miR-3175 in Glioma. PloS One (2015) 10: e0142387. doi: 10.1371/journal.pone.0142387
9. Zha Y, Cuevas IC, Gabriel RA, Su H, Nishimura S, Gao P, et al. Restoring Transcription Factor HoxA5 Expression Inhibits the Growth of Experimental Hemangiomas in the Brain. J Neuropathol Exp Neurol (2009) 68:626–32. doi: 10.1097/NEN.0b013e3181a91ce
10. Zhang L, He A, Chen B, Bi I, Chen J, Guo D, et al. A HOTAIR Regulatory Element Modulates Glioma Cell Sensitivity to Temozolomide Through Long-Range Regulation of Multiple Target Genes. Genomics Res (2020) 30:155–63. doi: 10.1101/gr.251058.119
11. Angelopoulou E, Paudel YN, Piperi C. Critical Role of HOX Transcript Antisense Intergenic RNA (HOTAIR) in Gliomas. J Mol Med (Berlin Germany) (2020) 98:1525–46. doi: 10.1007/s00109-020-01998-x
12. Li L, Wang Y, Song G, Zhang X, Gao S, Liu H. HOX Cluster-Embedded Antisense Long Non-Coding RNAs in Lung Cancer. Cancer Lett (2019) 450:14–21. doi: 10.1016/j.canlet.2019.02.036
13. Lin S, Zhang R, An X, Li Z, Fang C, Pan R, et al. lncRNA HOXA-AS3 Confers Cisplatin Resistance byInteracting With HOXA3 in Non-Small-Cell Lung Carcinoma Cells. Oncogenesis (2019) 8:60. doi: 10.1038/s41389-019-0170-y
14. Cheng S, Qian F, Huang Q, Wei L, Fu Y, Du Y. HOX4A, Down-Regulated in Lung Cancer, Inhibits the Growth, Motility and Invasion of Lung Cancer Cells. Cell Death Dis (2018) 9:665. doi: 10.1038/s41419-018-0497-x

FUNDING

The research was supported by grants from the National Natural Science Foundation of China No. 81871911 (WH), No. 81972237 (LX), and No.81772623 (LX), and the National Key Research and Development Program of China 2018YFC1312103 (LX).
29. Yung A, Chen J, Feng W, Qiao C, Han W, Nie Y, et al. Interleukin-1β-Mediated HOXC10 Overexpression Promotes Hepatocellular Carcinoma Metastasis by Upregulating PDKF1 and VASP. Theranostics (2020) 10:3833–48. doi: 10.7150/thno.41712

30. Lv X, Li L, Lv L, Xu Q, Jin S, Li K, et al. HOXD9 Promotes Epithelial-Mesenchymal Transition and Cancer Metastasis by ZEB1 Regulation in Hepatocellular Carcinoma. J Exp Clin Cancer Res: CR (2015) 34:133. doi: 10.1186/s13046-015-0245-3

31. Liao Y, Wang C, Yang Z, Liu W, Yuan Y, Li K, et al. Dysregulated Sp1/miR-130b-3p/HOXA5 Axis Contributes to Tumor Angiogenesis and Progression of Hepatocellular carcinoma. Theranostics (2020) 10:5209–24. doi: 10.7150/thno.43640

32. Liu L, Li Y, Deng H, Zhang C, Pu Y, Qian L, et al. MiR-193a-3p Promotes the Multi-Chemosensitivity of Bladder Cancer by Targeting the HOX9 Gene. Cancer Lett (2015) 357:105–13. doi: 10.1016/j.canlet.2014.11.002

33. Meng L, Xing Z, Guo Z, Liu Z. LINC01106 Post-Transcriptionally Regulates ELK3 and HOXD8 to Promote Bladder Cancer Progression. Cell Death Dis (2020) 11:1063. doi: 10.1038/s41419-020-03236-9

34. de Bessa Garcia SA, Araujo DG, Almeida MA, Vasconcelos L, Lopes RM, et al. Expression Is Elevated in Breast Cancer and Is Transcriptionally Regulated by Estradiol. Expression Is Elevated in Breast Cancer and Is Transcriptionally Regulated by Estradiol. J Cell Physiol (2020) 235:3579–91. doi: 10.1002/jcp.29246

35. Sun S, Wu Y, Guo W, Guo W, Kong L, Ren Y, et al. STAT3/HOTAIR Signaling Mediates HOXC10 Overexpression Promotes Hepatocellular Carcinoma. Mol Ther Nucleic Acids (2020) 11:1063. doi: 10.1038/s41419-020-03236-9

36. Sun S, Wu Y, Guo W, Guo W, Kong L, Ren Y, et al. STAT3/HOTAIR Signaling Mediates HOXC10 Overexpression Promotes Hepatocellular Carcinoma. Mol Ther Nucleic Acids (2020) 11:1063. doi: 10.1038/s41419-020-03236-9

37. Zhang Y, Yang C, Zhang M, Liu H, Gong C, Zhang J, et al. Interleukin HOTAIR Enhances ER Signaling and Confers Tamoxifen Resistance in Breast Cancer. Oncogene (2015) 35:3746–55. doi: 10.1038/onc.2015.340

38. Zhang Y, Yuan C, Li S, Chen Z, Sun M. LncRNA HOTAIR Influences Cell Growth, Migration, Invasion, and Apoptosis via the miR-20a-5p-HMGA2 Axis in Breast Cancer. Cancer Med (2018) 7:842–55. doi: 10.1002/cam4.1353

39. Lin J, Zhu H, Hong L, Tang W, Wang J, Hu H, et al. Coexpression of HOXA6 and PBX2 Promotes Metastasis in Gastric Cancer. Aging (2021) 13:6606–24. doi: 10.18632/aging.202426

40. Sun M, Nie F, Wang Y, Zhang Z, Hou J, He D, et al. LncRNA HOX11-AS Promotes Proliferation and Invasion of Gastric Cancer by Scaffolding the Chromatin Modification Factors PRC2, LSD1, and DNM1L. Cancer Res (2016) 76:6299–310. doi: 10.1158/0008-5472.Cancer Res-2016-2283-4

41. Zhang E, Han L, Yin D, He X, Hong J, Li X, et al. H3K27 Acetylation by EZH2 Promotes Metastasis in Gastric Cancer. J Biol Chem (2020) 295:10562–73. doi: 10.1074/jbc.S1203022000000000

42. Zhao W, Geng D, Li S, Chen Z, Sun M. HOXC10 Overexpression Promotes Hepatocellular Carcinoma Metastasis by Caspases 2 and 8. Mol Cell Biol (2014) 24:924–35. doi: 10.1128/mcb.24.2.924-935.2004

43. Zhang Z, Guo L, Li H, Liu Y, Xu L, Chen J, et al. HOX Genes and the Epithelial-Mesenchymal Transition as a Potential Therapeutic Option in Esophageal Squamous Cell Carcinoma. Cancer Sci (2019) 110:1735–45. doi: 10.1111/cas.13993

44. Ding WJ, Zhou M, Chen MM, Qu CY. HOXB8 Promotes Tumor Metastasis and the Epithelial-Mesenchymal Transition via ZEB2 Targets in Gastric Cancer. J Cancer Res Clin Oncol (2017) 143:385–97. doi: 10.1007/s00432-016-2283-4

45. Zhang E, Han L, Yin D, He X, Hong J, Li X, et al. H3K27 Acetylation Activated Long-Non-Coding RNA CCT1A Affects Cell Proliferation and Migration by Regulating SPRY4 and HOXB13 Expression in Esophageal Squamous Cell Carcinoma. Nucleic Acids Res (2017) 45:3086–101. doi: 10.1093/nar/gkw1247

46. Li J, Tong G, Huang C, Luo Y, Wang S, Zhang Y, et al. HOX10 Promotes Cell Migration, Invasion, and Tumor Growth in Gastric Carcinoma Cells Through Upregulating Proinflammatory Cytokines. J Cell Physiol (2020) 235:3579–91. doi: 10.1002/jcp.29246

47. Zhang Q, Yuan C, Li S, Chen Z, Sun M. LncRNA HOTAIR Enhances Acetylation of Histone H3K27. J Exp Clin Cancer Res: CR (2019) 38:412. doi: 10.1186/s13046-019-1399-1

48. Yuan C, Zhu X, Han Y, Song C, Liu C, Su S, et al. Elevated HOXA1 Expression Correlates With Accelerated Tumor Cell Proliferation and Poor Prognosis in Gastric Cancer Partially via Cyclin D1. J Exp Clin Cancer Res: CR (2016) 35:15. doi: 10.1186/s13046-016-0294-2

49. Niinuma T, Suzuki H, Nojima M, Nosho K, Yamamoto H, Takamaru H, et al. HOXC8 Regulates Self-Renewal, Differentiation and Transformation of Gastrointestinal Stromal Tumors. Cancer Res (2012) 72:1126–36. doi: 10.1158/0008-5472.Can-11-003

50. Chen Z, Wu D, Thomas-Ahner JM, Lu C, Zhao P, Zhang Q, et al. Diverse AR-V7 Cistromes in Castration-Resistant Prostate Cancer Are Governed by
69. Zhou J, Yang X, Song P, Wang H, Wang X. HOXC6 in the Prognosis of Prostate Cancer. Oncogene (2014) 33:4558–67. doi: 10.1038/onc.2013.404

70. Xu F, Shangguan X, Pan J, Yue Z, Shen K, Ji Y, et al. HOXD13 Suppresses Prostate Cancer Metastasis. Proc Natl Acad Sci USA (2019) 116:15. doi: 10.1073/pnas.1812989116

71. Ewing CM, Ray AM, Lange EM, Zuhlke KA, Robbins CM, Tembe WD, et al. Germline Mutations in HOXB13 and Prostate-Cancer Risk. Nat Engl J Med (2012) 366:141–7. doi: 10.1056/NEJMoa1100000

72. Chen J, Zhu S, Jiang N, Shang Z, Quan C, Niu Y. HOXB3 Promotes Prostate Cancer Cell Progression by Transactivating CDC4. Cancer Lett (2013) 330:217–24. doi: 10.1016/j.canlet.2012.11.035

73. Idiakadar P, Morgan R, Michael A. HOX Genes in High Grade Ovarian Cancer. Cancers (2019) 11:1107. doi: 10.3390/cancers11081107

74. Miller KR, Patel IN, Zhang Q, Norris EJ, Boelsma J, Michener C, et al. HOXA4/HOXB3 Gene Expression Signature as a Biomarker of Recurrence in Patients With High-Grade Serous Ovarian Cancer Following Primary Cytoreductive Surgery and First-Line Adjunctive Chemotherapy. Gynecologic Oncol (2018) 149:155–62. doi: 10.1016/j.ygyno.2018.01.022

75. Ko SY, Naora H. HOXA9 Promotes Homotypic and Heterotypic Cell Interactions That Facilitate Ovarian Cancer Dissemination via Its Induction of P-Cadherin. Mol Cancer (2014) 13:170. doi: 10.1186/1476-4598-13-170

76. Nakayama I, Shibazaki M, Yashima-Abo A, Miura F, Sugiyama T, Masuda T, et al. Downregulating the Activity of the Wnt/β-Catenin Pathway and Transactivating TP53. Cell Death Dis (2020) 11:420. doi: 10.1038/s41419-020-2629-3

83. Wang Y, Cui N, Zheng PS. HOX5A Inhibits the Proliferation and Neoplasia of Cervical Cancer Cells via Downregulating the Activity of the Wnt/β-Catenin Signaling Pathway. Cell Death Dis (2021) 12:105. doi: 10.1038/s41419-021-03411-6

84. Ma HM, Cui N, Zheng PS. HOX5A Inhibits the Proliferation and Neoplasia of Cervical Cancer Cells via Downregulating the Activity of the Wnt/β-Catenin Pathway and Transactivating TP53. Cell Death Dis (2020) 11:420. doi: 10.1038/s41419-020-2629-3

85. Falini B, Brunetti L, Sponzilli P, Martelli MP. NPM1-Mutated Acute Myeloid Leukemia: From Bench to Bedside. Blood (2020) 136:1707–21. doi: 10.1182/blood.2019004226

86. Zhang H, Zhang Y, Zhou X, Wright S, Hyle J, Zhao L, et al. Functional Interrogation of HOXA9 Regulome in MLLr Leukemia via Reporter-Based CRISPR/Cas9 Screen. eLife (2020) 9. doi: 10.7554/eLife.57858

87. Mohr S, Doebeler C, Comoglio F, Berg T, Beck J, Bohnenberger H, et al. HOXA9 and Meis1 Cooperatively Induce Addiction to Syk Signaling by Suppressing miR-146a in Acute Myeloid Leukemia. Cancer Cell (2017) 31:549–562.e11. doi: 10.1016/j.ccell.2017.03.001

88. de Bock CE, Demeyere S, Deyguy S, Verbeke D, Sweer D, Geelen R, et al. HOXA9 Cooperates With Activated JAK/STAT Signalling to Drive Leukaemia. Development. Cancer Discov (2018) 8:1616–31. doi: 10.1158/2159-8290.Cd-17-0583

89. Whelan JT, Ludwig DL, Bertrand FE. HOX9 Induces Insulin-Like Growth Factor–1 Receptor Expression in B-Lineage Acute Lymphoblastic Leukemia. Leukemia (2008) 22:1161–9. doi: 10.1038/leu.2008.57

90. Yoshino S, Yokoyama T, Sunami Y, Takahara T, Nakamura A, Yamazaki Y, et al. Trib1 Promotes Acute Myeloid Leukemia Progression by Modulating the Transcriptional Programs of HOXA9. Blood (2021) 137:75–88. doi: 10.1182/blood.201904856

91. Wang H, Jia XH, Chen JR, Yi Y, Wang Y, Li YJ, et al. HOXB4 Knockdown Reduces Multidrug Resistance of Human Myelogenous Leukemia K562/ADM Cells by Downregulating P-Gp, MRP1 and BCRP Expression of P-Adaptin. Jpn J Cancer Res (2016) 97:2529–37. doi: 10.3892/jjc.2016.3738

92. Calvo KR, Knoepfle PS, Sykes DB, Pasillas MP, Kamps MP. Meis1 Suppresses Differentiation by G-CSF and Promotes Proliferation by SCF: Potential Mechanisms of Cooperation With Hoxa9 in Myeloid Leukemia. Proc Natl Acad Sci USA (2001) 98:13110–5. doi: 10.1073/pnas.23115398

93. Bi L, Zhou B, Li H, He L, Wang C, Wang Z, et al. A Novel miR-375–HOXB3–SCDC3–DNMT3B Regulatory Circuitry Contributes to Leukemogenesis in Acute Myeloid Leukemia. BMC Cancer (2018) 18:182. doi: 10.1186/s12885-018-4097-z

94. Quiré R, Karlsson G, Hertwig F, Rissler M, Lindqvist B, Fioretos T, et al. Sma3B binds Hox9 in the Cytoplasm and Protects Primitive Hematopoietic Cells Against Nuclear Activation by Hoxa9 and Leukemia Transformation. Blood (2011) 117:9591–30. doi: 10.1182/blood-2010-08-301879

95. Daniels TR, Necatoc II, Rodriguez JA, Pandha HS, Morgan R, Penichet ML. Disruption of HOX Activity Leads to Cell Death That Can be Enhanced by the Interference of Iron Uptake in Malignant B Cells. Leukemia (2010) 24:1555–63. doi: 10.1038/leu.2010.145

96. Sarkar D, Leung EY, Baguley BC, Finlay GJ, Askarian-Azar ME. Epigenetic Regulation in Human Melanoma: Past and Future. Epigenetics (2015) 10:103–21. doi: 10.1080/15592294.2014.1003746

97. Wardwell-Ojgo J, Dogruulk T, Gifford A, Zhang Y, Heffernan TP, van Doorn R, et al. HOX11 Drives Melanoma Tumor Growth and Metastasis and Elicits an Invasion Gene Expression Signature That Prognosticates Clinical Outcome. Oncogene (2014) 33:1017–26. doi: 10.1038/onc.2013.30

98. Morgan R, Simpson G, Gray S, Gillett C, Tabi Z, Spicer J, et al. HOX Translation Factors Are Potential Targets and Markers in Malignant Mesothelioma. BMC Cancer (2016) 16:835. doi: 10.1186/s12885-016-1016-7

99. Gaunt SJ, Hox Cluster Genes and Colinearities Throughout the Tree of Animal Life. Int J Dev Biol (2018) 62:673–83. doi: 10.3878/jdb.1801629g

100. Lewis EB. A Gene Complex Controlling Segmentation in Drosophila. Nature (1978) 276:565–70. doi: 10.1038/276565a

101. Quinonez SC, Innis JW. Human HOX Gene Disorders. Mol Genet Metab (2014) 111:4–15. doi: 10.1016/j.ymge.2013.10.012

102. Paço A, Aparecida de Bessa Garcia S, Leitão Castro J, Costa-Pinto AR, Freitas R, Roles of the HOX Proteins in Cancer Invasion and Metastasis. Cancers (2020) 13:10. doi: 10.3390/cancers13010010

103. Li B, Huang Q, Wei GH. The Role of HOX Transcription Factors in Cancer Predisposition and Progression. Cancers (2019) 11:528. doi: 10.3390/cancers11040528

104. Kuo TL, Cheng KH, Chen LT, Hung WC. Deciphering The Potential Role of Hox Genes in Prostate Cancer. Cancers (2019) 11:734. doi: 10.3390/cancers11050734

Frontiers in Oncology | www.frontiersin.org
October 2021 | Volume 11 | Article 770428
146. Wang L, Yao J, Yu T, Zhang D, Qiao X, Yao Z, et al. Homeobox D3, A Novel Link Between Bone Morphogenetic Protein 9 and Transforming Growth Factor Beta 1 Signaling. J Mol Biol (2020) 432:2030–41. doi: 10.1016/j.jmb.2020.01.043

147. Yang MH, Zhao L, Wang L, Ou-Yang W, Hu SS, Li WL, et al. Nuclear lncRNA HOXD-AS1 Suppresses Colorectal Carcinoma Growth and Metastasis via Inhibiting HOXD3-Induced Integrin β3 Transcriptional Activating and MAPK/AKT Signalling. Mol Cancer (2019) 18:31. doi: 10.1186/s12935-019-0955-9

148. Yachi K, Tsuda M, Kohnaka S, Wang L, Oda Y, Tanikawa S, et al. miR-23a Promotes Invasion of Glioblastoma via HOXD10-Regulated Glial-Mesenchymal Transition. Signal transduction targeted Ther (2018) 3:33. doi: 10.3310/sdt0312-0053-6

149. Liu T, Song Y, Chen X, Li P, Wang T, Yang C, et al. HOXB6 Inhibits EMT and Promotes Invasion of Glioblastoma Multiforme in the Proximal and Distal Colon Cancer Pathogenesis. J Mol Cancer (2019) 3:33. doi: 10.1186/s12943-018-0822-0

150. Li Y, Ren Y, Wang Y, Tan Y, Wang Q, Cai J, et al. A Compound AC1IQQWB Selectively Disrupts HOX-Targeted Recruitments of PRC2 and Enhances Cancer Therapy of DZNep. Theranostics (2019) 9:4608–23. doi: 10.7150/thno.35188

151. Choe J, Suh S, Kim S, Lee H, Lee YK, Lee Y, et al. Unique Significance of HOXB9 Acetylation at K27 Is Responsible for Its Suppression of Colon Cancer Progression. Cancer Lett (2018) 426:63–72. doi: 10.1016/j.canlet.2018.04.002

152. Morgan R, Boxall A, Harrington KJ, Simpson GR, Gillett C, Michael A, et al. Targeting the HOX/PBX Dimer in Breast Cancer. Breast Cancer Res Treat (2012) 136:389–98. doi: 10.1007/s10549-012-2259-2

153. Palakurthy RK, Wajapeeyee N, Santra MK, Gaizn C, Lin L, Gobeil S, et al. EPigenetic Silencing of the RASSF1A Tumor Suppressor Gene Through HOXB3-Mediated Induction of DNM3B Expression. Mol Cell (2009) 36:219–30. doi: 10.1016/j.molcel.2009.10.009

154. Lorton BM, Shechter D. Cellular Consequences of Arginine Methylation. Mol Cell (2007) 10:269–73. doi: 10.1016/s1097-2765(07)90198-9

155. Morgan R, Boxall A, Harrington KJ, Simpson GR, Gillett C, Michael A, et al. Targeting the HOX/PBX Dimer in Breast Cancer. Breast Cancer Res Treat (2012) 136:389–98. doi: 10.1007/s10549-012-2259-2

156. Del Bene F, Wittbrodt J. Cell Cycle Control by Homeobox Genes in Development and Disease. Semin Cell Dev Biol (2005) 16:449–60. doi: 10.1016/j.semcdb.2005.02.001

157. Yu M, Zhan J, Zhang H. HOX Family Transcription Factors: Related Signaling Pathways and Post-Translational Modifications in Cancer. Cell Signal (2020) 66:109469. doi: 10.1016/j.cellsig.2019.109469

158. Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, et al. HOX Transcript Antisense RNA (HOTAIR) Promotes Invasion of Glioblastoma Multiforme. Semin Cell Dev Biol (2019) 45:61–7. doi: 10.1016/j.semcdb.2019.04.016

159. Qu X, Alsaqr S, Zhuo Y, Shan B. HOX Transcript Antisense RNA (HOTAIR) Promotes Invasion of Glioblastoma Multiforme. Semin Cell Dev Biol (2019) 45:61–7. doi: 10.1016/j.semcdb.2019.04.016

160. Li Y, Ren Y, Wang Y, Tan Y, Wang Q, Cai J, et al. A Compound AC1IQQWB Selectively Disrupts HOX-Targeted Recruitments of PRC2 and Enhances Cancer Therapy of DZNep. Theranostics (2019) 9:4608–23. doi: 10.7150/thno.35188

161. Qu X, Alsager S, Zhuo Y, Shan B. HOX Transcript Antisense RNA (HOTAIR) Promotes Invasion of Glioblastoma Multiforme. Semin Cell Dev Biol (2019) 45:61–7. doi: 10.1016/j.semcdb.2019.04.016

162. Tan SK, Pastori C, Penas C, Komotor RJ, Ivan ME, Wahlestedt C, et al. Serum Long Noncoding RNA HOTAIR as a Novel Diagnostic and Prognostic Biomarker in Glioblastoma Multiforme. Mol Cancer (2018) 17:74. doi: 10.1186/s12943-018-0822-0

163. Quagliata L, Matter MS, Piscocchio S, Arabi L, Ruiz C, Procino A, et al. Long Noncoding RNA HOTTIP/HOXA13 Expression Is Associated With Disease Progression and Predicts Outcome in Hepatocellular Carcinoma Patients. Hepatol (Baltimore Md.) (2014) 59:911–23. doi: 10.1002/hep.26740

164. Procino A. Class I Homeobox Genes, “The Rosetta Stone of the Cell Biology”, in the Regulation of Cardiovascular Development. Curr medicinal Chem (2016) 23:263–75. doi: 10.2174/0929867323666151207113102

165. Selleri L, Zappavigna V, Ferretti E. Building a Perfect Body: Control of Vertebrate Organogenesis by PBX-Dependent Regulatory Networks. Genes Dev (2019) 33:2358–75. doi: 10.1101/gad.318774.118

166. Hoshino Y, Hayashida T, Hirata A, Takahashi H, Chiba N, Ohmura M, et al. Bevacizumab Terminates Homebox B9-Induced Tumor Proliferation by Silencing Microenvironmental Communication. Mol Cancer (2014) 13:102. doi: 10.1186/1476-4593-13-102

167. Song J, Wang T, Xu W, Wang P, Wan J, Wang Y, et al. HOXB9 Acetylation at K27 Is Responsible for Its Suppression of Colon Cancer Progression. Cancer Lett (2018) 426:63–72. doi: 10.1016/j.canlet.2018.04.002

168. Morgan R, Boxall A, Harrington KJ, Simpson GR, Gillett C, Michael A, et al. Targeting the HOX/PBX Dimer in Breast Cancer. Breast Cancer Res Treat (2012) 136:389–98. doi: 10.1007/s10549-012-2259-2

169. Rajagopal T, Talluri S, Akhlaya RL, Dunna NR. HOTAIR lncRNA: A Novel Oncogenic Propellent in Human Cancer. Clinica Chimica Acta; Int J Clin Chem (2020) 503:1–18. doi: 10.1016/j.cca.2019.12.028

170. Tatangelo F, Di Mauro A, Scognamiglio G, Aquino G, Lettiero A, Delrio P, et al. Posterior HOX Genes and HOTAIR Expression in the Proximal and Distal Colon Cancer Progression. J Trans Med (2018) 16:350. doi: 10.1186/s12967-018-1725-y

171. Singh A, Trivedi P, Jain NK. Advances in siRNA Delivery in Cancer Therapy. Artif Cells Nanomedicine Biotechnol (2018) 46:274–83. doi: 10.1080/21691401.2017.1307210

172. Mantra MFL, Bolognese A, Basilicata MG, Pepe G, Campiglia P, Procino A. Novel Anticancer Drug SH-Pyro[3,2-a] Phenoxazin-5-One (PPH) Regulates lncRNA HOTAIR and HOXC Genes in Human MCF-7 Cells. Bahrain Med Bull (2021) 43:334–41

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.