Review

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Contributions of HOX genes to cancer hallmarks: Enrichment pathway analysis and review

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Abstract

Homeobox genes function as master regulatory transcription factors during development, and their expression is often altered in cancer. The HOX gene family was initially studied intensively to understand how the expression of each gene was involved in forming axial patterns and shaping the body plan during embryogenesis. More recent investigations have discovered that HOX genes can also play an important role in cancer. The literature has shown that the expression of HOX genes may be increased or decreased in different tumors and that these alterations may differ depending on the specific HOX gene involved and the type of cancer being investigated. New studies are also emerging, showing the critical role of some members of the HOX gene family in tumor progression and variation in clinical response. However, there has been limited systematic evaluation of the various contributions of each member of the HOX gene family in the pathways that drive the common phenotypic changes (or "hallmarks") and that underlie the transformation of normal cells to cancer cells. In this review, we investigate the context of the engagement of HOX gene targets and their downstream pathways in the acquisition of competence of tumor cells to undergo malignant transformation and tumor progression. We also summarize published findings on the involvement of HOX genes in carcinogenesis and use bioinformatics methods to examine how their downstream targets and pathways are involved in each hallmark of the cancer phenotype.

Keywords

HOX genes, transcription factors, embryogenesis, hallmarks of cancer

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Background

HOX genes are members of the major homeobox gene family of transcription factors that encode a highly conserved 61-amino-acid helix-turn-helix DNA binding homeodomain.[1,2] In mammals, there are 39 HOX genes that are highly conserved at the genomic level and are organized tandemly in four clusters—each one mapped on different chromosomes: HOXA on chromosome 7, HOXB on chromosome 17, HOXC on chromosome 12, and HOXD on chromosome 2.[3] Homeobox genes were first discovered after genetic characterization of *Drosophila melanogaster* mutants that led to distinct

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homeotic displacement of body parts to different locations.[4]

The discovery of the homeobox genes was crucial for understanding the genetic control of early development. HOX proteins function as master regulators of embryonic development acting through a complex assembly with other transcription factors and with cofactor proteins.[5] HOX genes define cellular territories during the formation of the anteroposterior axis on the embryogenesis in many different organisms. This highly coordinated temporospatial control of several cellular processes including proliferation, differentiation, migration, and apoptosis led to the HOX family to be classed as selector genes.[6] The HOX regulatory mechanism has affinity for the cognate binding of the homeodomain to specific sequence elements of target genes. Also, it has a very versatile function due to its context-dependent activity since it can activate or repress downstream pathways in a tissue-specific manner.[7] The versatility of these transcription factors is a result of their unique regulation, which is determined by the linear order of each gene along the chromosome. HOX genes are arranged within clusters so that the position of a gene in the 3′ to 5′ direction corresponds to the temporal sequence and spatial order of gene expression in the anteroposterior axis of the organism. This form of developmental regulation is a standard feature in vertebrates, called temporal and spatial collinearity.[8] Although there is a large amount of information about HOX genes in embryonic development, it is important to note that these transcription factors have diverse functions since they regulate pathways in many different cellular processes. Evidence shows that HOX genes are also expressed in adulthood, suggesting that they continue to play a role in cellular identity for tissue maintenance and stem cell renewal[9–12] and can be expressed in cancer stem cells.[12] As critical regulatory genes in mammalian development, the HOX family has pathophysiological functions, which have been intensely studied by the scientific community.

Mutations in HOX genes are associated with several human developmental disorders, including limb malformation such as synpolydactyly (SPD),[13] hand-foot-genital syndrome (HFGS),[14] and Charcot–Marie–tooth disease (CMT).[15] Deregulation of HOX genes has also been identified in cancer.[16–18] Several studies reported differences between normal and tumor conditions as reviewed by Bathlekar et al.[12] and also the role of HOX genes in cancer susceptibility and progression;[19] however, assigning a specific role for HOX genes as drivers of the malignant phenotype requires further investigation. Evidence that HOX genes may be deregulated in different ways in different types of cancer is accumulating. The mechanisms that cause deregulation of these genes in tumors appear to vary; sometimes HOX transcripts appear to be downregulated and in other situations they are upregulated. These findings imply that factors related to tissue specificity may lead to HOX genes acting as tumor suppressor genes in some cell types, while in others, they might be more involved in oncogenic effects.[20,21]

HOX genes seem to undergo deregulation by at least three different mechanisms. The first way is through tumor-specific loss of control of the spatiotemporal patterns of expression in comparison with the expression that is usually seen in related normal tissues. The second mechanism is through gene dominance. This type of HOX gene deregulation occurs in a tumor, but the corresponding normal tissue does not usually express the HOX gene. The third mechanism is due to epigenetic alterations that lead to loss of control due to methylation changes at regulatory regions of HOX genes.[22] Through these three mechanisms, HOX genes become disrupted and can influence a large number of pathways that are crucial for proliferation and maintenance during tumor growth. As proposed by Hanahan and Weinberg, cancer has a highly complex etiology that begins when a normal cell acquires some essential new capability for tumorigenesis that will allow it to develop the cancer phenotype. These so-called capabilities or "hallmarks of cancer" encompass sustained proliferative signaling, insensitivity to anti-growth signals, resistance to cell death, limitless reproductive potential, immune system evasion, sustained angiogenesis, and invasion and metastasis potential. All these steps are triggered by enabling characteristics such as genomic instability and tumor-promoting inflammation.[23,24] This review highlights the role of the HOX genes in the regulation of the hallmarks of cancer by reviewing recent literature and by an enrichment pathway analysis based on their target genes and pathways.

Review strategy

We investigated the downstream HOX gene targets and pathways in which they are involved to determine how the deregulation of the HOX family can interfere with each of the hallmarks of cancer. Our overall strategy was to search for targets of human HOX genes using transcription factor databases and then to perform a gene set enrichment analysis (GSEA) based on these targets (Figure 1). The enriched gene set was then used to identify biological processes associated with the cancer hallmarks that could be affected by HOX target pathways. We reasoned that by applying this strategy, we could assign each HOX gene to specific cancer hallmarks. We extract target data from tftargets package available in https://github.com/slowkow/tftargets. The database assembles data from five other databases, which are TRED,[25] ITFP,[26] Neph2012,[27] TRRUST,[28] and Marbach.[29] After generating the target list for each

Table 1. Top five HOX genes associated with the hallmarks of cancer.

Hallmarks	HOX members				
Sustaining proliferative signaling	*HOXC4*	*HOXB2*	*HOXB3*	*HOXC6*	*HOXA13*
Resisting cell death	*HOXB9*	*HOXB2*	***HOXB5***	***HOXA9***	*HOXC8*
Inducing angiogenesis	*HOXC9*	*HOXC5*	***HOXB6***	***HOXA2***	*HOXB7*
Activating invasion and metastasis	*HOXD1*	*HOXA1*	*HOXA2*	*HOXB7*	*HOXA3*
Genome instability and mutation	***HOXC12***	***HOXC11***	*HOXC5*	*HOXB2*	*HOXA9*
Tumor-promoting inflammation	*HOXA1*	*HOXD1*	*HOXC11*	*HOXC9*	*HOXC13*
Deregulating cellular energetics	*HOXA4*	*HOXA5*	*HOXB6*	*HOXB4*	*HOXC5*
Avoiding immune destruction	*HOXD1*	*HOXA1*	*HOXC9*	***HOXD10***	***HOXA10***

Genes *HOX* in bold type contain targets with similar scores within the hallmark.

one of the 39 HOX genes (shown in Supplemental Table S2), we used the GSEA method to identify the biological process pathways enriched by those targets.[30] Within GSEA, we used the Molecular Signature Database, selecting specifically the hallmark gene set collection (MSigDB Collection: H). For the biological pathway selection, we applied the false discovery rate (FDR) q-value <0.05 and used the top 20 enriched pathways. After that, each pathway in GSEA was assigned to a specific hallmark, and we ranked HOX genes whose target list showed the highest number of occurrence of pathways related to each of the hallmarks, according to our assignment (Supplemental Table S3). Table 1 shows the top five HOX genes highly associated with each hallmark of cancer. The consensus of the target genes by hallmarks is listed in Supplemental Table S3. Interestingly, only two cancer hallmarks—evasion of growth suppressors and replicative immortality—did not have an association with HOX gene targets based on this enrichment approach.

HOX genes contributing to cancer cell capabilities

Sustaining proliferative signaling

Normal cells will usually proliferate when supplied with appropriate stimuli for cell growth, such as mitogenic factors, but tumor cells show a reduced dependence on exogenous proliferation signals.[23] Several HOX genes are deregulated in many cancer types and play critical roles in tumor proliferation.[31–41] Our enrichment analysis showed that *HOXC4, HOXB2, HOXB3, HOXC6*, and *HOXA13* exhibited the highest number of enriched targets involving pathways related to sustained proliferative signaling (Table 1). The five HOX genes have either tumor-suppressive or tumor-promoting properties, depending on which tumor type they are expressed. We found that *HOXC4* had more targets enriched in proliferation pathways in keeping with studies that have shown its involvement in stem cell expansion[42] and lymphocyte proliferation.[43] However, there are presently no reports of a direct influence of *HOXC4* on tumor cell growth. Interestingly, Frasor et al.[44] demonstrated that *HOXC4* is upregulated by estradiol stimulation of breast cancer cells. This hormone is associated with initiation and proliferation in breast cancer cells,[45] indirectly suggesting a role for *HOXC4* in breast cancer growth. In a study of acute myeloid leukemia, *HOXB2* was identified as one of the negative regulators of FLT3-internal tandem duplication (ITD)-dependent proliferation.[46] Similarly, a functional screen for novel repressors of breast cancer tumorigenesis identified *HOXB2* as a growth inhibitor.[47] In prostate cancer, *HOXB3* was shown to bind to the cell division cycle associated 3 (*CDCA3*) promoter region, transactivating its expression and promoting proliferation[31] (Figure 2). Transcriptional silencing of *HOXB3* expression has also been shown to promote proliferation and invasion in glioblastoma.[32] It was demonstrated that *HOXC6* is capable of promoting cell proliferation and colony formation in gastric cancer cell lines, allowing tumor cells to grow in both an anchorage-dependent and independent way.[34] In contrast, overexpression of *HOXC6* in prostate cancer cell lines strongly reduced tumor cell growth.[35] Luo et al.[48] identified, by high-throughput chromosome conformation capture (Hi-C) analysis, a loop between a prostate cancer risk region with the *HOXA13* gene. The anchor point from the repressive loop region was removed using the CRISPR/Cas9 system. The lack of that resulted in positive regulation of *HOXA13*, leading to transcriptome changes, including oncogene overexpression.[48] Both *HOXA13* and *HOTTIP* promoted cell proliferation and growth and were associated with a higher grade of gliomas.[37] In addition to these top five HOX genes, several other members of the gene family were shown to be involved in the proliferation of different types of cancer. Li et al.[38] demonstrated that *HOXA7* has an essential role in the regulation of cell cycle progression in hepatocellular carcinoma (Figure 2). It was also found that aberrant expression of *HOXB9* inhibited the differentiation of acute myeloid progenitor cells and maintained the undifferentiated and rapidly proliferative state of

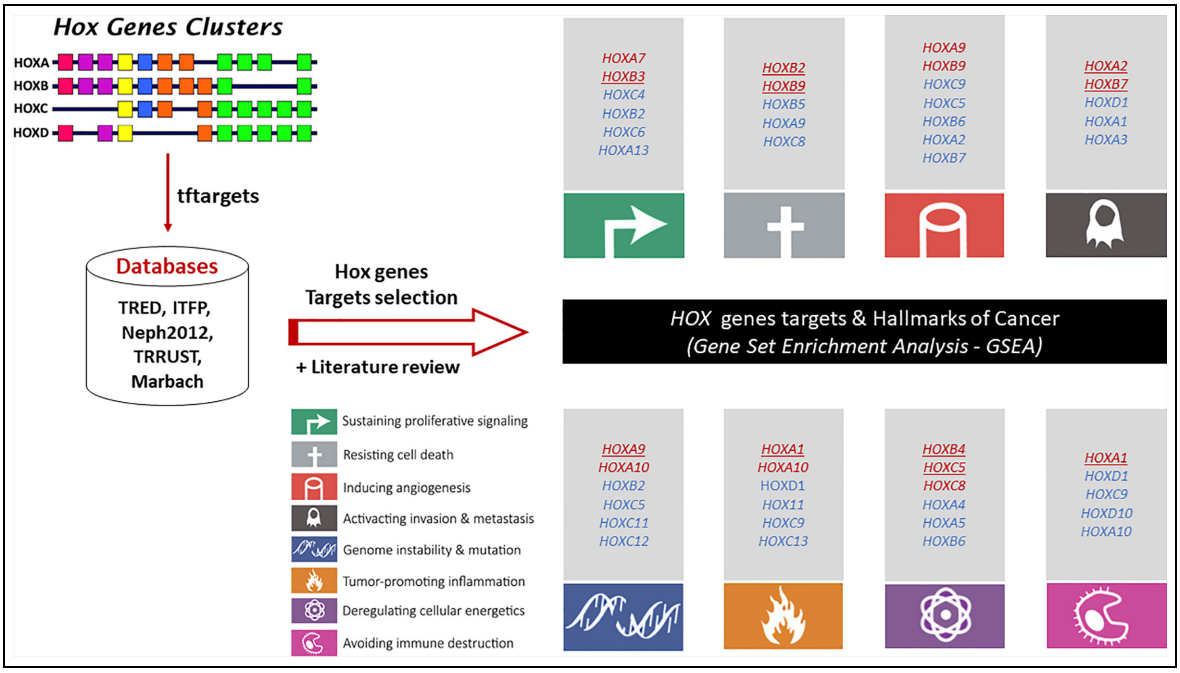

Figure 1. Workflow showing the step-by-step experimental design to select the top five HOX genes predicted to regulate eight hallmarks of cancer. In red are the genes presented in Figure 2, and the underlined genes are those in the top five presented in Table 1.

leukemic cells.[39] Similarly, other examples can be found, such as *HOXB7* in breast cancer,[40,49,50] *HOXA4* and *HOXA9* in colorectal cancer,[41] and *HOXC8* in epithelial ovarian cancer.[33]

Evading growth suppressors

A crucial growth control mechanism disrupted by the loss of tumor suppression is limitless replication and evasion of growth arrest.[51] Curiously, in our analysis, no HOX genes had targets enriched for this particular hallmark. However, there are a few studies that have explored the role of individual HOX genes in the regulation of genetic pathways related to cell growth control. For example, in prostate cancer, *HOXB13* can contribute to tumorigenesis by inhibiting p21, a cyclin kinase inhibitor involved in the control of cell proliferation and differentiation (Figure 2).[52] It has also been shown that a prostate cancer risk-associated rs339331 single-nucleotide polymorphism (SNP) is within a functional *HOXB13* binding site. The risk-associated allele in rs339331 enhances the binding of *HOXB13* to a transcription enhancer, conferring allele-specific upregulation of the *RFX6* gene, a gene that is related to prostate cancer cell proliferation and migration.[53,54] Similarly, Carbone et al.[55] showed that *HOXB9* mediates resistance to treatment with a vascular endothelial growth factor (*VEGF*) inhibitor in colorectal cancer. In another study, Hakami et al.[56] demonstrated that *HOXD10* suppresses miR-146a expression in head and neck squamous cell carcinoma (HNSCC) (Figure 2). Loss of growth control occurred because miR-146a is a well-known inhibitor of cell proliferation and a metastasis suppressor.[56] The onset of ovarian cancer may be involved in pathways mediated by *HOXA10* expression. This HOX gene was shown to confer a growth advantage to ovarian surface epithelial cells, by enhancing cell adhesion, probably by overexpressing αvβ3 integrin and preventing anoikis in target cells for tumorigenesis.[57]

Resisting cell death

The response to physiological cell death may contribute either positively or negatively to tumor development. In cancer, both apoptosis and autophagy are mainly impaired by loss of function of tumor suppressor genes or by modulating expression of pro-apoptotic or anti-apoptotic factors, which may lead to immortalization of cancer cells.[24] Necrosis, on the other hand, will enhance the pro-tumoral activity by releasing bioactive regulatory factors which will stimulate neighboring cells to proliferate, contributing to tumor progression.[23,24] According to our data, *HOXB9, HOXB2, HOXB5, HOXA9*, and *HOXC8* were the five HOX genes that targeted signaling pathways that were the most related to the hallmark of resisting cell death (Table 1). In addition to those genes, *HOXA13* and *HOXB13* are also known to be associated with evasion of apoptosis.[58–62] *HOXB9* expression has been reported as significantly increased

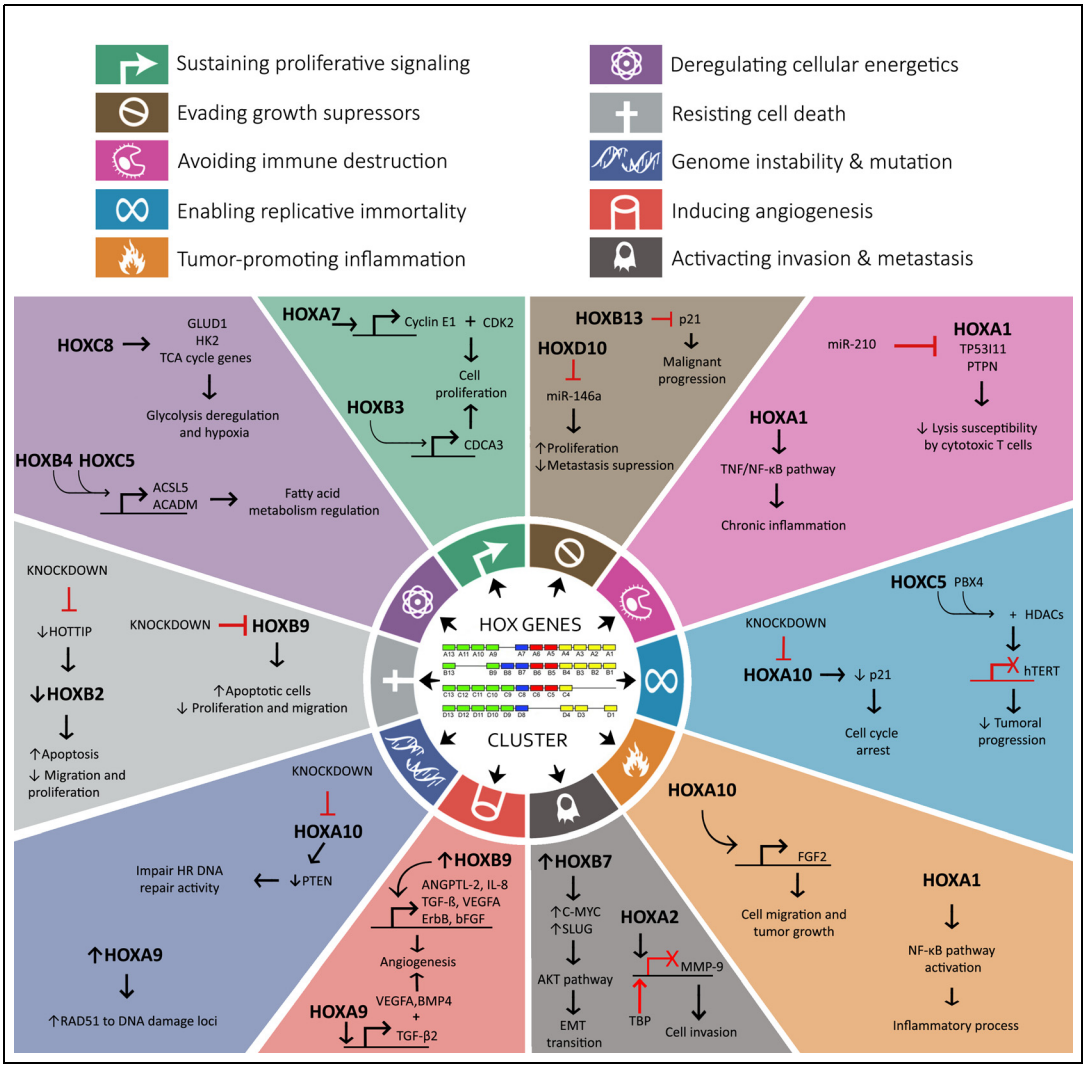

Figure 2. HOX genes in the hallmarks of cancer. HOX genes positively (black arrows) or negatively (red) regulate the expression of genes involved in cancer pathways.
Modified from Hanahan and Weinberg.[24]

in tumor tissues and to be associated with a poor prognosis, chemotherapy resistance, invasion, and metastasis.[63–65] Vychytilova-Faltejskova et al.[66] showed in their recent study that *HOXB9* downregulation in p53-proficient colorectal cell lines led to significant increases in the number of apoptotic cells and decreased proliferation and migration rates (Figure 2). However, depending on the type of tumor, the anti-apoptotic activity of *HOXB9* could be associated either with oncogenic or with tumor suppressor activities.[66] In acute myeloid leukemia, loss of expression of *HOXB2* is associated with an enrichment of oncogenic pathways, and its overexpression decreased cell proliferation and further increased apoptosis rates.[46] In contrast, *HOXB2* overexpression in pancreatic cancer was associated with a poor prognosis.[67] It has been also demonstrated that the knockdown of *HOTTIP*, another HOX-associated long non-coding RNA (lncRNA) that has pro-oncogenic functions similar to those reported for *HOTAIR*, promotes the downregulation of *HOXB2*, which induced apoptosis and decreased cell proliferation and migration[68] (Figure 2). The *HOXB5* gene also has anti-apoptotic activity, which was first observed by Kam et al.[69] Their study showed that *HOXB5* regulated neural crest development *in vivo*, by repressing apoptosis through directly inducing Foxd3.[69] Although *HOXB5* is well known as an oncogene and is overexpressed in many cancer types,[70–72] it has been shown that *HOXB5* is repressed in the oral squamous cell[73] and ovarian and papillary thyroid carcinomas. Its downregulation and repression were associated with methylation or microRNA (miRNA) regulation.[74,75] Both *HOXB5* and *HOXA9* have been reported to have anti-apoptotic activity in human astrocytes, glioblastoma, and leukemia cells and to be

associated with increased proliferation.[76,77] It has also been shown that *PI3K* may reduce *HOXA9* expression since a decrease in *PI3K* activity led to a reduction in *HOXA9* transcript levels.[76,78] *PI3K* is well known as a regulator of cell growth, survival, and proliferation, and the *PI3K* downregulation is also associated with autophagy and/or apoptosis induction.[24,79] *HOXC8* has been reported as a potential oncogene, regulating many genes involved in tumor progression. Its expression is associated with cell proliferation, migration inhibition, and induction of apoptosis in ovarian and laryngeal squamous cancer cells. *HOXC8* serves as a cadherin-11 (*CDH11*)-specific transcription factor, and as expected, its expression is associated with increased *CDH1*-dependent metastatic potential [33,80–83]. In chondrocytes, depletion of HOXc8 protein decreased proliferation rates (probably associated with increased cell death), and M-phase appeared to be prolonged with cell cycle arrest.[84] In addition to the five HOX genes associated with the hallmark of cell death, *HOXA13* and *HOXB13* have also been reported to be involved in apoptosis modulation. In prostate tumors, *HOXA13* overexpression promoted tumor cell proliferation, migration, and invasion and inhibited tumor cell apoptosis, which was correlated with an unfavorable survival.[58] *HOXA13* is also upregulated in gastric cancer tissues, and its expression has been directly correlated with Wnt/β-catenin activation, which explains how its increased expression enhances cell proliferation and invasion rates and decreases rates of cell apoptosis in cancer cells.[59,60] Conversely, *HOXB13* is a known activator of apoptotic pathways, and HOXb13 loss-of-function mutations are highly associated with an increased risk of prostate cancer related to increased levels of cell proliferation and decreased rates of apoptosis.[61,62,73,85,86] Collectively, the HOX genes that are involved in cell death responses can act as oncogenes or as tumor suppressor genes. Their functional relationship to this cancer hallmark will depend on the specific role the HOX gene had in maintaining cellular homeostasis in normal tissues.[85]

Enabling replicative immortality

Cancer cells acquire immortality by escaping from the limitations on the total number of cell cycle divisions that can occur before senescence, non-proliferative state, crisis, and apoptosis take place. There are several mechanisms involved in cellular immortalization, including telomere length stabilization, genomic instability, epigenetic gene silencing by selective promoter methylation, oxidative DNA damage, inactivation of cell cycle regulatory genes, or overexpression of cellular oncogenic proteins.[24]

Telomeres (chromosome ends) are essential for imposing a replication limit. Telomerase is a ribonucleoprotein enzyme involved with integrity of chromosome ends.[78] This catalysis occurs by adding new DNA repetitive sequences (TTAGGG) to the 3′ ends of the telomeres. The telomerase enzyme complex consists of a protein component hTERT (human telomerase reverse transcriptase) and an RNA molecule, which serves as a template for the enzymatic complex to ensure the maintenance of telomeres. The hTERT activity has a restricted profile, and its expression has a tight correlation with telomerase activity. In somatic cells, telomerase expression is strongly repressed, resulting in telomere shortening throughout replication cycles.[79] About 85% of human cancers show TERT expression reactivation. This way, cancer cells can reactivate TERT expression as a mechanism to bypass the process of cellular senescence by extending cell life span and thus supporting tumor proliferation and progression.[80]

The role of the HOX genes on these mechanisms is unclear. In our analysis, we did not identify any enrichment of the *HOX* target genes in the replicative immortality hallmark. There is a report that knockdown of *HLX1* (H2.0-like homeobox 1) and *HOXA9* repressed INK4a expression by recruiting *HDAC1* and polycomb repressive complex (*PCR2*), promoting cell cycle arrest and senescence in leukemia.[87] Zhang et al.[88] have also shown that *HOXA10* knockdown decreases p21 expression and promotes cell cycle arrest in endometrial cancer(Figure 2). It is well known that telomerase is activated in cancer cells and hTERT inhibition suppresses cell proliferation.[89,90] Yan et al.[91] demonstrated a strong negative correlation between *HOXC5* and *hTERT* expression in thymoma and testicular germ cell tumor. They identified that *HOXC5* overexpression decreased *hTERT* expression in cancer cells, and the *HOXC5* knockdown increased hTERT expression and telomerase elongation. hTERT regulation by *HOXC5* involved transcriptional regulation by promoting the *HOXC5:PBX4* complex formation by recruiting histone deacetylase (HDAC) proteins to repress hTERT expression in cancer cells[91](Figure 2). These findings were the first to suggest that HOX genes play a role in telomerase shortening and telomere dysfunction in cancer cells, leading to inhibition of cell proliferation.

Inducing angiogenesis

Angiogenesis is the process by which new blood vessels are formed to provide nutrients and oxygen for adequate cell function and survival of normal and tumor tissues. Tumors acquired the ability of sustained angiogenesis by counterbalancing the positive and negative signals to activate or inhibit this process.[24] Several HOX genes have been shown to promote sustained angiogenesis by activating VEGF signaling pathways or by inhibiting TSP-1 (thrombospondin-1), the main respective inducers and inhibitors of angiogenesis.[92] The result of our enrichment analysis with *HOX* target genes against the GSEA hallmarks shows that the

HOX genes most associated with angiogenesis were *HOXC9, HOXC5, HOXA2, HOXB6*, and *HOXB7* (Table 1). Among the HOX genes upregulated in tumors and associated with the activation of angiogenesis is *HOXB7*, which activates gene expression of fibroblast growth factor (bFGF) and many other pro-angiogenic factors such as vascular endothelial growth factor A (VEGFA), interleukin-8 (IL-8), and angiopoietin-2 (ANGPT2) in breast cancer cell lines[93] and in multiple myeloma cells.[94] Activation of pro-angiogenic factors has also been associated with *HOXB9*, which is upregulated in breast carcinoma.[95] Similarly, *HOXB13* upregulates pro-angiogenic factors in pancreatic carcinoma.[96] Integrin signaling and extracellular matrix proteases also contribute to the balance between pro- and anti-angiogenic factors.[23] An important HOX gene that is associated with these pathways is *HOXD3*, which promotes tumor-specific angiogenesis through upregulating expression of αvβ3 integrin, urokinase plasminogen activator (uPA), and integrin α5β1. Promotion of tumor blood vessels occurs in tumors but not in quiescent endothelial cells.[97,98]*HOXC9* was suggested to have a role in quiescence of endothelial cells and to negatively regulate tumor angiogenesis by inhibition of IL-8.[99] This growth factor is closely involved in angiogenesis since it has been demonstrated to contribute to enhanced blood vessel density in tumors[100] and it acts as an autocrine growth factor produced by tumor cells.[101]*HOXA9* is also involved in multiple mechanisms of angiogenesis activation in ovarian cancer. It has been shown to upregulate transforming growth factor-β2 (*TGF-β2*), which together with *VEGFA* and *BMP4* has been suggested to influence RUNX1T1-regulated angiogenesis.[102,103] Furthermore, the expression of *HOXA9* by progenitor endothelial cells was demonstrated to influence gene regulation of essential endothelial genes such as *eNOS, VEGFR2*, and VE-cadherin in the tumor microenvironment, which are essential for angiogenesis.[104] We also found an association of *HOXB3* with angiogenesis in cancer, verified in canine hemangiosarcoma samples.[105]

Activating invasion and metastasis

Invasion and metastasis are the leading cause of mortality in patients with cancer. Recent studies have identified several gene targets and molecular pathways that underlie both these complex processes.[24] We focused on the top five HOX genes that had targets enriched for invasion and metastatic pathways. Our data analyses ranked *HOXD1, HOXA1, HOXA2, HOXB7*, and *HOXA3* genes in decreasing order for target enrichment (Table 1). *HOXD1* has previously been shown to have increased expression in ovarian cancer in comparison with control ovarian tissue, suggesting that its activation may be associated with ovarian carcinoma development.[106]*HOXA1* is a known oncogene[107] that can be targeted and inhibited by miR-100, resulting in the inhibition of downstream genes *MET, SMO*, and *SEMA3C*, all of which have been implicated in lower rates of cell migration and invasion.[108] Other studies illustrate diverse regulation of *HOXA1* gene by miRNAs and also demonstrate an association with invasiveness and metastasis, which includes miR-10 family members in pancreatic cancer, gastric cancer, and cervical cancer;[109–111] miR-30 family members in esophageal cancer and giant cell tumor of bone;[112,113] miR-99a in nasopharyngeal carcinoma and breast cancer;[114,115] and miR-433 in colon cancer.[116] Similar regulation occurs for *HOXB3*, which is targeted by multiple miRNAs, such as the miR-375 that inhibits cancer stem cell traits by degrading *HOXB3* messenger RAN (mRNA) in breast cancer.[117]*HOXB3* is also inhibited by specific targeting and degradation by the miR-10 family, leading to upregulation of metastasis in pancreatic cancer[118] and increased invasion in endometrial cancer.[119] Interestingly, Li et al.[120] demonstrated that *HOXA2* promotes cell invasion by degradation of extracellular components in nasopharyngeal carcinoma, competing with TATA-box binding protein (TBP) for TATA-box near metalloproteinase-9 (*MMP-9*) transcription start site and thus repressing *MMP-9* expression (Figure 2). Recent studies have shown that the *HOXB7* gene may contribute to malignant progression and metastasis by direct binding and activation of *TGFβ2* in breast cancer[121] or through activation of TGF-β/SMAD3 signaling in lung adenocarcinoma.[122] Overexpression of *HOXB7* has also linked to activation of the AKT pathway via upregulation of c-Myc and Slug, resulting in epithelial-to-mesenchymal transition and malignant progression of hepatocellular carcinoma[123](Figure 2). In another study, Wang et al.[124] demonstrated that *HOXB7* may also have a critical role in cell invasion through the activation of the MAPK/ERK pathway in hepatocellular carcinoma.

Promotion of genome instability and mutation

Underlying the cancer cell features, there is genome instability, which promotes the genetic diversity that will contribute to the acquisition of the hallmarks. Tumors have diverse progression and proliferation profiles as well as defects in genomic maintenance, cell cycle control, and errors in DNA repair machinery, all of which favor carcinogenesis.[24]

The top five HOX genes most associated with genomic instability and DNA repair pathways after the enrichment analysis were *HOXC12, HOXC11, HOXC5, HOXB2*, and *HOXA9* (Table 1). Although there is good evidence that these HOX genes are involved in cancer development, their role in DNA repair and genomic instability is presently unknown.

Some studies suggest that *HOXC12, HOXC11*, and *HOXC5* play a role in cellular proliferation and epigenetic modifications.[91,125–127] The *HOXC12* gene has been assumed to be a tumor suppressor gene since it is inactivated in HNSCC and lymphomas due to somatic mutations and alterations on DNA methylation.[125,128] The methylation of a CpG island located between *HOXC11* and *HOXC12* is positively correlated with *HOTAIR* lncRNA expression, which is associated with increased proliferation and cancer progression and also with unfavorable outcomes in breast cancer patients.[126,127] The *HOXC5* gene has been associated with both replicative immortality and cellular metabolic pathways, as discussed more extensively elsewhere in this review.[91,129] Cohesins comprise a crucial mitotic protein complex that regulates the separation and segregation of chromatids and safeguards genome stability during cell division. Manini et al.[130] evaluated cohesins and found that among other genes, *HOXB2* was significantly downregulated when the cells were depleted for SMC1B cohesin. Leunen et al.[131] compared BRCA-related ovarian cancer to sporadic ovarian tumors. Both *BRCA1* and *BRCA2* play a crucial role in homologous repair (HR) of double-stranded breaks on DNA (DSBs). The *BRCA1* ovarian tumors were characterized by complex alterations affecting the HOX gene cluster, with some genes being upregulated and others downregulated, suggesting they had different contributions to the instability processes in ovarian cancer.[131] In another study, *HOXA9* expression correlated with HR gene expression and DNA repair, with overexpression being significantly increased when there was recruitment of RAD51 to DNA damage foci. These data suggest that *HOXA9* might act as an upstream regulator of *RAD51* in acute leukemia cell lines[132] (Table 1). Other studies showed that the loss of *HOXA9* resulted in an increased radiation sensitivity in mice and that *HOXA9* gene was also found to be silenced by methylation in more than half of the cases of ovarian carcinomas.[74,133] As discussed above, *HOXA9* is also involved in other hallmarks of cancer such as sustained proliferative signaling, apoptosis, or resistance to cell death pathways[134] (Table 1 and Supplemental Table S1).

In addition to the top five HOX genes found in our enrichment analysis, *HOXA10* and *HOXB7* have both been described as having a role in DNA repair and genomic stability maintenance. *HOXA10* has been reported as a regulator of the nuclear function of *PTEN*, a tumor suppressor gene that is known to be involved in aspects of DNA repair. Kim et al.[135] demonstrated that after *HOXA10* knockdown, the expression of *PTEN* in the nucleus was significantly reduced, and impaired HR DNA repair activity was observed (Figure 2). In agreement with these data, the high expression levels of *HOXA10* and *HOXA9* were associated with shorter survival times in pediatric high-grade glioma patient.[136] Similarly, in breast cancer cell lines, *HOXB7*-expressing cells was related to better survival after irradiation exposure, probably due to interactions with proteins involved in DNA DSB repair that act as genomic caretakers.[137] *HOXB7* promoted an enhanced non-homologous end joining (NHEJ) activity, an error-prone DNA repair pathway. However, the increased NHEJ mutation rate may lead to decreased genomic stability, suggesting that *HOXB7* may also lead to oncogene activations during progression. Overexpression of *HOXB7* has also been associated with increased proliferation rates and invasive characteristics in ovarian cancer cells.[138] Some HOX gene clusters may contribute differently to the various pathways of genome stability and maintenance, and these functional characteristics may be useful as therapeutic targets.

Tumor-promoting inflammation

Chronic inflammation can cause DNA damage and lead to cancer development due to alterations in cellular and molecular events such as altered proliferative rates, resistance to apoptosis, neovascularization, epigenetic events, and changes in gene expression.[139–142] The inflammatory process involves the activation of innate immunity in response to oxidative stress and/or the stimulation of the nuclear factor κB (NF-κB) pathway.[139] In many types of cancer, NF-κB activation has been associated with an inflammatory response, and tumor initiation and progression.[143] In our enrichment pathway analysis, we identify the *HOXA1, HOXD1, HOXC11, HOXC9*, and *HOXC13* genes as the top five *HOX* highly associated with the inflammatory process in cancer (Table 1). Some HOX genes have previously been reported to be involved in tumor-promoting inflammation and other tumor-enabling characteristics. For instance, *HOXA1* promotes the activation of the NF-κB pathway in breast cancer cells. This transcription factor acts upstream of IκB and by triggering *TAB2, IκBα, IKKα/β*, and p65 phosphorylation. The collective regulation of these pathways suggests that activation of the NF-κB pathway by *HOXA1* overexpression can promote the inflammatory process in breast cancer cells[144] (Figure 2). We did not find any evidence that *HOXD1* participated in tumor inflammatory processes. However, Guo et al.[145] have shown that *HOXD1* participates in the inflammatory process when activated by the nerve growth factor (NGF)/tropomyosin-related kinase A receptor (TrKA) pathway during development in the mouse. Interestingly, we found that 53 out of 1945 *HOXD1* targets are involved in the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway (unpublished data). In addition, the lnRNA *HOXD-AS1*, localized between

HOXD1 and *HOXD3*, regulates the expression of genes correlated with the inflammatory process by the JAK/STAT pathway in neuroblastoma cells.[146] These data implicate the participation of *HOXD1* during tumor inflammation by regulation of the JAK/STAT pathway. Wang et al.[147] demonstrated that the expression levels of *HOXC8, HOXC9, FABP4*, and *HSL* were inversely correlated with *TNFα* and *MCP-1* levels in adipose tissue adjacent to malignant breast tumors. These findings suggest that low levels *HOXC9* increased the cytokine expression and led to the participation of this gene in the inflammatory process.[147] *HOXA10* overexpression increases the *FGF2* levels in myeloid progenitor cells by Triad1-induced ubiquitination and degradation of Fgf-R1.[148,149] In *HOXA10* knockout mice, the opposite result was demonstrated, with decreased levels of Fgf2 in *HOXA10*-deficient mice and an increase in granulocyte/monocyte cells that promoted an inflammatory response during leukemogenesis[148,149] (Figure 2). We were unable to find published evidence in current literature indicating that *HOXC13* participated directly in tumor-promoting inflammation. Its identification by our enrichment analysis as one of the top five genes in this hallmark may mean that other functions related to inflammation have yet to be determined.

Deregulating cellular energetics

Metabolic reprogramming of tumor cells has been indicated as a hallmark of cancer since Otto Warburg pointed out that even in the presence of oxygen, cancer cells reprogram their metabolism, relying more on glycolysis than oxidative phosphorylation (OXPHOS).[150] Although this metabolic switch does not seem efficient to ATP production, it supports the elevated biomass demands of the highly proliferative cells typical of cancer.[24] So far, only one study has associated an HOX gene with the metabolic reprogramming in cancer. Jiang et al.,[151] showed that latent membrane protein 1 (LMP1), one of the oncoproteins of the Epstein–Barr virus (EBV), represses HOX to maintain tumor growth. A direct role of the *HOXC8* gene in energy metabolism was shown by restoring *HOXC8* expression. Ectopic expression of *HOXC8* arrested tumor growth and downregulated glycolytic enzymes, such as GLUD1 and HK2, and upregulated tricarboxylic acid (TCA) cycle–related genes. Enrichment analysis using HOX target genes showed that, in addition to *HOXC8*, other HOX members are also involved in energetic metabolism. Here, we show that *HOXA4, HOXA5, HOXB6, HOXB4*, and *HOXC5* could modulate different metabolic pathways such as oxidative phosphorylation, fatty acid metabolism, adipogenesis, and glycolysis (Table 1). Corroborating these findings, Cantile et al.[152] showed that *HOXA4* was involved in adipocyte differentiation. In addition, both *HOXB4* and HOXC5 regulate the enzymes ACSL5 and ACADM: the former is responsible for activating long-chain fatty acids for lipid synthesis and beta-oxidation degradation, and the latter is involved in the first step of peroxisomal beta-oxidation.[152] Similarly, *HOXA5* is known to regulate *ACOX1*, which acts in the first step of the mitochondrial beta-oxidation. Fatty acid metabolism has been described as an alternative energy source for the cancer cells, and HOX genes might play an important role in regulating this pathway.[153]

HOX genes also appear to regulate OXPHOS and glycolysis, two metabolic pathways commonly altered in cancer cells.[154] In normal cells under normoxia, glucose is converted to pyruvate and then to acetyl-CoA, which undergoes oxidation in the TCA cycle, generating the electron transporters NADH and $FADH_2$. These molecules feed the electron respiratory chain, formed by five mitochondrial complexes, which are held in the OXPHOS structures in the inner mitochondrial membrane.[154,155] Our in silico analysis based on transcription factor databases showed that many genes coding for subunits of mitochondrial complexes are regulated by *HOXB4* and *HOXC5*, especially concerning the ATP synthase complex that is responsible for the ATP synthesis. Altered subunit expression can impact OXPHOS functioning and decrease ATP production.[129] In addition, key glycolysis and hypoxia genes, such as *HK1, CDKN1A*, and *PPARGC1A*, are regulated by *HOXA5*. In normal cells, hypoxia triggers metabolic rewiring using the hypoxia-inducible factor (HIF)-1, which induces the expression of genes associated with metabolism and angiogenesis.[156] Many HOX targets are involved in this pathway, suggesting an association of HOX and hypoxia response, which could have both metabolic and pro-tumorigenic consequences. Although HOX genes have been commonly deregulated in different cancer types, not much is known regarding the role of the HOX family in energy metabolism. Our findings show that HOX could modulate different metabolic pathways and support the metabolic rewiring inherent to cancer cells (Table 1). However, more studies employing both genomic and metabolic tools are necessary to unravel details of the role of HOX genes in tumor metabolism.

Avoiding immune destruction

Despite protecting the host from tumor cells, the loss of the immune system can also contribute to the development of a tumor.[157] Tumor cells can evade immune cell surveillance by downregulating the antigen-processing machinery. This evasion is mediated by the production of immunosuppressive cytokines (by tumor cells or from surrounding cells in the tumor microenvironment), which in turn activate immunosuppressive cells like

Tregs, and by promoting tolerance or apoptosis in T-cells.[158] These processes support immunoediting—the selection of tumor cells resistant to immune system components, which contributes to tumor development.[157,158] Nevertheless, not much is known about the role of HOX genes in facilitating tumor cell evasion of immune destruction. Noman et al.[159] reported that miR-210, which is induced under hypoxic conditions in lung cancer and melanoma, targets *PTPN1, HOXA1*, and *TP53I11* genes, which, in turn, decreased tumor cell susceptibility to cytotoxic T-lymphocyte-mediated lysis. Sio et al.[160] demonstrated that mammary tumor cells produce granulocyte colony-stimulating factor (G-CSF), which acts together with hematopoietic regulatory cytokines FLT3L and granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance hematopoietic stem and progenitor cell (HSPC) production. This treatment caused global and gene-specific changes in histone methylation patterns associated with enhanced *HOXA9* gene expression in bone marrow cultures. As a result, activated bone marrow cells and progenitors of hematopoietic origin could instigate the growth of indolent tumors and metastases.[160,161] Taminiau et al.[144] showed that there is a highly significant positive correlation between expression of *HOXA1* and of members of the tumor necrosis factor (TNF)/NF-κB signaling pathway in breast tumors and that *HOXA1* can activate NF-κB in a transcription-independent manner. NF-κB is a nuclear factor that promotes inflammation by activation of proinflammatory cytokines and also has a role in cancer initiation, development, metastasis, and resistance to treatment.[162] As chronic inflammation can lead to the promotion of tumor cell growth and angiogenesis,[158]*HOXA1* has a potential role in evasion of the immune system in breast cancer. Most of the targets from *HOXA1*, which was found to be one of the most enriched HOX genes associated with immune evasion in this work, are enriched to TNFα signaling via the NF-κB pathway. Among those targets are genes that are subunits from NF-κB complex, such as *NFKB1* and *REL*,[163] or genes that are also activated by this complex, including *CCL2, CCL20*, and *PTGS2*.[164–166] These findings corroborate the critical role of *HOXA1* in this pathway. In summary, as specific HOX genes can be deregulated in different ways depending on tumor type or site,[167] their role in tumor destruction evasion seems to be similarly dependent both on the type of tumor and on the genes that are being regulated.

Conclusion and future perspectives

Although the involvement of HOX genes in tumorigenesis is well known, there has been no study systematically evaluating their various roles in cancer progression in the context of the global functions of their target genes. As previously mentioned, the HOX genes act in different biological processes, which include proliferation, differentiation, migration, and apoptosis.[6] Their role in regulating these processes may continue during carcinogenesis by modulation of the cancer hallmarks.[168] In this review, we employed a strategy analyzing the collective functions of each HOX gene's regulatory pathways to investigate the direct link between their potential roles in the various cancer hallmark phenotypes. Thus, we can infer in which genetic mechanisms the HOX genes would be most likely to act. The HOX genes present quite variable aberrant expression in different tumor types. In this review, we showed that the 39 members of the HOX family regulate a large number of targets that are differently enriched in biological pathways. These pathways can be associated with each of the cancer hallmarks. The diverse role of HOX genes is a reflection of their versatility as a transcription factor, since they regulate the most diverse targets, displaying a broad biological role within cells. In addition, its multifunctional role can be explained by interaction with transcriptional cofactors. For example, HOX genes (paralog groups 1–8) linked to PBX transcription show higher affinity and specificity to DNA sequences.[169] Interestingly, inhibition of this interaction can be accomplished by the use of HXR9 peptides that mimic an HOX protein hexapeptide, leading to the antagonism of HOX/PBX formation.[170] Thus, HOX genes can be used as therapeutic targets by the use of this peptide.[171]

In conclusion, the studies presented here corroborate the idea that they may have a dual function with oncogenic or tumor suppressor potential. Further studies are necessary to address whether the deregulation of HOX genes is the cause or a consequence of carcinogenesis. Indeed, a better understanding of how HOX genes and their downstream pathways are involved in each cancer is likely to bring new insights for the development of specific tumor biomarkers and new therapeutic approaches that target the most clinically important hallmarks.

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Author contributions

D.B.B., A.D.D.S., I.I.B., S.C.S.C., B.R.M., C.C., J.A.S., and L.F.A. wrote the manuscript. J.R.P. conducted in silico analysis for HOX gene targets. D.B.B., A.D.D.S., I.I.B., S.C.S.C., B.R.M., C.C., and L.F.A. conducted gene set enrichment analysis. L.G. set up Supplementary Table 1. D.B.B. coordinated the review drafting. A.R. contributed to the writing. W.A.S.

supervised and contributed to the writing structure of the manuscript. All authors reviewed and approved the final manuscript.

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Ethical approval

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Supplemental material

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