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Homeobox Gene Deregulation: Impact on the Hallmarks of Cancer

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Abstract

Homeobox genes comprise a super-family of evolutionarily conserved genes that play essential roles in controlling body plan specification and cell fate determination. Substantial evidence indicates that leukemogenesis is driven by abnormal expression of homeobox genes that control hematopoiesis. In solid tumors, aberrant expression of homeobox genes has been increasingly found to modulate diverse processes such as cell proliferation, cell death, metastasis, angiogenesis and DNA repair. This review discusses how homeobox genes are deregulated in solid tumors and the functional significance of this deregulation in the hallmarks of cancer.

Keywords

homeobox genes; transcription factors; solid tumors; tumorigenesis; hallmarks

1. Introduction

Homeobox genes were first discovered in *Drosophila* by the ability of their mutations to cause formation of body parts in inappropriate contexts (Gehring & Hiromi, 1986; McGinnis & Krumlauf, 1992). In humans, mutations in homeobox genes cause a wide range of complex developmental abnormalities including limb malformations and sensory defects (Mortlock & Innis, 1997; Ruf et al., 2004). Most of our current understanding of the functions of homeobox genes in mammalian embryonic development has come from studies of knock-out mice. Different sets of homeobox genes control skeletal patterning, limb and craniofacial morphogenesis, and development of virtually all organ systems (McGinnis & Krumlauf, 1992; Panganiban & Rubenstein, 2002; Christensen et al., 2008). In adults, homeobox genes also regulate tissue regeneration, and play critical roles in controlling self-renewal and differentiation of hematopoietic progenitors (Argiropoulos & Humphries, 2007).

1.1. Genomic organization of mammalian homeobox genes

Mammalian homeobox genes are categorized into several families that are named after their homologs in the fly. Examples include *DLX* (*distal-less*), *PAX (paired)*, *MSX* (*muscle*

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segment), *CDX* (*caudal), EN (engrailed)* and *OTX* (*orthodenticle*). The evolution of homeobox gene families and the phylogenetic relationships between family members have been the focus of extensive study (Sumiyama et al., 2003; Garcia-Fernàndez, 2005; Lemons & McGinnis, 2006). Most homeobox genes are dispersed throughout the genome, whereas the members of the mammalian *HOX* and *DLX* gene families are organized in clusters. The *HOX* family comprises 39 genes that are tandemly arranged in four clusters (*HOXA, HOXB, HOXC, HOXD*) located on different chromosomes (McGinnis & Krumlauf, 1992; Pearson et al., 2005). The six members of the *DLX* family are arranged in bigene clusters that are located upstream of the *HOX* clusters (Sumiyama et al., 2003). The temporal and spatial expression of *HOX* genes is tightly coupled to their clustered physical organization. In general, *HOX* genes that are located at the 3′ end of the clusters are expressed early in development and in anterior body regions, whereas the genes at the 5′ end of clusters are expressed later and in more posterior body regions (McGinnis & Krumlauf, 1992; Pearson et al., 2005).

1.2. Structural features of homeoproteins

Proteins that are encoded by homeobox genes are often called ‘homeoproteins’ and are widely regarded to function as transcription factors (Gehring et al., 1994; Biggin & McGinnis, 1997). A few homeoproteins also exhibit non-transcriptional activities such as controlling mRNA export, translation and protein stability (Dubnau & Struhl, 1996; Topisirovic et al., 2005; Aoki et al., 2011). A hallmark of homeoproteins is their DNA-binding domain, termed the homeodomain, which binds DNA elements containing a TAAT motif (Gehring et al., 1994). The helix-turn-helix structure of the homeodomain is highly conserved across homeoproteins. Binding affinity and specificity of homeoproteins for different target gene promoters is mediated by diversity in their amino acid residues and by interactions with other transcription factors (Gehring et al., 1994; Biggin & McGinnis, 1997; Chariot et al., 1999). Transcriptional target selectivity of homeoproteins is also mediated by additional conserved motifs that are unique to different families. For example, HOX proteins contain a motif that mediates interactions with PBX co-factors (Chang et al., 1995). PAX proteins contain an additional, signature DNA-binding domain called the paired domain (Robson et al., 2006), whereas ZEB family members contain zinc finger domains in addition to the homeodomain (Vandewalle et al., 2009).

2. Mechanisms that cause homeobox gene deregulation in tumors

Overexpression or down-regulated expression of many homeobox genes has been observed in a wide variety of malignancies (Abate-Shen, 2002; Samuel & Naora, 2005; Shah & Sukumar, 2010). Translocation-induced fusions of *HOX* genes in hematologic malignancies are well-documented (Samuel & Naora, 2005; Argiropoulos & Humphries, 2007). One example is the t(7;11)(p15;p15) translocation in acute myeloid leukemia that results in the fusion of the HOXA9 protein to the amino-terminus of the nuclear pore complex protein NUP98 (Borrow et al., 1996; Nakamura et al., 1996). In contrast to hematologic malignancies, the mechanisms that cause homeobox gene deregulation in solid tumors are less understood. Translocations that result in fusion of PAX3 and PAX7 to the FKHR transcription factor have been identified in alveolar rhabdomyosarcoma (Galili et al., 1993;

Davis et al., 1994). Translocation-induced fusion of PAX8 to the peroxisome proliferator-activated receptor γ1 (PPARγ1) occurs in thyroid follicular tumors (Kroll et al., 2000). However, as discussed below, deregulation of other homeobox genes in solid tumors has been attributable to other types of genomic aberrations and to epigenetic mechanisms.

2.1. Loss of heterozygosity and gene amplification

Several homeobox genes with tumor-suppressive properties localize to 'hotspots' that undergo loss of heterozygosity (LOH) in cancers [Table I]. One example is *NKX3.1* that maps to 8p21. This region is deleted in ~80% of prostate cancers (He et al., 1997) and also frequently undergoes allelic loss in prostatic intraepithelial neoplasia (PIN) (Emmert-Buck et al., 1995). Inactivation of *Nkx3.1* in mice induces PIN-like lesions and cooperates with *Pten* loss to induce carcinoma (Kim et al., 2002a; Kim et al, 2002b). To date, only a few overexpressed homeobox genes have been found to localize to regions that are amplified in tumors. The *HOXB* gene cluster and the *DLX4* gene map to 17q21.3-q22, a region that is amplified in ~10% of breast cancers (Hyman et al., 2002). However, *HOXB7* and *DLX4* are over-expressed in >50% of breast cancers (Man et al., 2005; Wu et al., 2006), indicating that gene amplification is not the sole mechanism underlying the overexpression of these genes.

2.2. DNA methylation and chromatin modification

Aberrant methylation of CpG islands frequently occurs in tumors, and is the most commonly identified mechanism that silences expression of homeobox genes in solid tumors [Table II]. Many CpG islands within *HOX* gene clusters are methylated in lung cancers (Rauch et al., 2007). In a study by Tommasi and colleagues (2009), one third of the CpG islands that were identified in genome-wide analysis of DNA methylation to be hypermethylated in early-stage breast cancers were associated with homeobox genes. These authors also identified that ~50% of the hypermethylated genes overlapped with known Polycomb targets (Tommasi et al., 2009). Polycomb group proteins form multi-protein complexes that dynamically alter chromatin structure by modifying specific residues in histone tails and recruit DNA methyltransferases that methylate DNA (Mills, 2010). Polycomb-mediated repression is a principal mechanism by which *HOX* gene expression is tightly regulated during development (Soshnikova & Duboule, 2009). EZH2, a component of the Polycomb Repressive Complex 2 (PRC2), is overexpressed in breast cancers and several other types of solid tumors (Mills, 2010). Trithorax group proteins counteract Polycomb-mediated silencing and their levels are also altered in various cancers (Mills, 2010). Aberrant expression of Polycomb and Trithorax group proteins might therefore be an important mechanism by which multiple *HOX* genes are deregulated in tumors.

2.3. Non-coding RNAs

Repression of homeobox gene expression by non-coding RNAs has been the subject of extensive focus in the developmental biology field and has attracted increasing attention in the context of cancer. Long noncoding RNAs and microRNAs are present in the intergenic regions of *HOX* clusters and control *HOX* gene expression through both *cis*- and *trans*-acting mechanisms (Lemons & McGinnis, 2006; Yekta et al., 2008). One striking example is the long non-coding RNA *HOTAIR* that is located in the *HOXC* locus. *HOTAIR* interacts

with and targets PRC2 to the *HOXD* locus (Rinn et al., 2007). *HOTAIR* expression in primary breast tumors has been found to be a strong predictor of metastasis and promotes metastasis by inducing genome-wide re-targeting of PRC2 to an occupancy pattern resembling that of embryonic fibroblasts (Gupta et al., 2010). Several microRNAs have been identified that either promote or suppress tumor progression through targeting specific homeobox genes. *miR-10b* is highly expressed in metastatic breast cancer cells and promotes metastasis by inhibiting translation of *HOXD10* mRNA, resulting in increased expression of the pro-metastatic gene *RHOC* (Ma et al., 2007). Conversely, *miR-185* is down-regulated in breast cancer cells, and inhibits tumor cell growth by repressing *SIX1*, a homeobox gene that induces cyclin A1 expression (Imam et al., 2010). *miR-31* has been found to be down-regulated in cancer-associated fibroblasts (CAFs) and inhibits the ability of CAFs to stimulate tumor cell invasiveness by targeting the homeobox gene *SATB2* (Aprelikova et al., 2010).

3. Functional significance of homeobox genes in the established hallmarks of cancer

Studies to date have revealed that homeobox genes have either tumor-suppressive or tumor-promoting properties depending on the context of their expression (Abate-Shen, 2002; Samuel & Naora, 2005; Shah & Sukumar, 2010). The expression patterns and functional properties of homeobox genes in solid tumors fall into two broad categories. In the first category are homeobox genes whose expression is normally maintained in differentiated adult tissues, but is down-regulated in tumors [Figure 1]. These homeobox genes often exhibit tumor-suppressive properties. In the second category are homeobox genes that are expressed in tumors derived from tissues in which these genes are normally expressed during embryonic development (i.e. ‘reactivated’ or overexpressed as compared to the normal adult tissue type) [Figure 1]. Less commonly, homeobox genes can be expressed in tumors derived from a lineage in which these genes are not normally expressed during development. Homeobox genes that fall in this second category often have tumor-promoting properties. Despite numerous reports of their aberrant expression, the mechanisms of many homeobox genes in tumors are poorly understood. Whereas homeoproteins have highly selective functions *in vivo*, they exhibit promiscuous DNA-binding *in vitro* (Biggin & McGinnis, 1997) and consequently only a few *bona fide* transcriptional targets have been identified. However, recent studies have revealed a variety of mechanisms by which homeobox genes control key processes that constitute the core hallmarks of cancer.

3.1. Sustained proliferative signaling

The ability to sustain chronic proliferation is a well-established hallmark of cancer cells (Hanahan & Weinberg, 2000). One important mechanism by which proliferation is sustained is through autocrine stimulation by growth factors such as fibroblast growth factor-2 (FGF-2). HOXB7 induces transcription of the *FGF-2* gene and promotes growth of melanomas, breast and ovarian cancers (Caré et al., 1996; Caré et al., 1998; Naora et al., 2001). Several homeoproteins stimulate tumor cell growth by activating transcription of genes that promote cell cycle progression [Figure 2]. For example, DLX5 stimulates proliferation of lung cancer cells by directly activating c-*myc* transcription (Xu & Testa,

2009). DLX5 has also been found to stimulate ovarian cancer cell growth by activating transcription of the gene encoding insulin receptor substrate 2 (IRS-2), an oncogenic signaling adaptor protein, and thereby enhancing AKT signaling (Tan et al., 2010). Interestingly, HOXA9 has been reported to induce cyclin D1 expression in leukemic cells by binding the translation initiation factor eIF4E and stimulating eIF4E-dependent export of *cyclin D1* mRNA (Topisirovic et al., 2005).

3.2. Evasion of growth-suppressors

In addition to sustaining growth-promoting signals, cancer cells circumvent signals that inhibit growth (Hanahan & Weinberg, 2000). Several homeoproteins transcriptionally activate genes that induce cell cycle arrest and their expression is decreased in tumors [Figure 2]. CDX2 inhibits proliferation of intestinal epithelial cells and its expression is down-regulated in colorectal tumors (Ee et al., 1995). CDX2 induces expression of the cyclin-dependent kinase (CDK) inhibitor $p21^{WAF1/Cip1}$ through transcriptional activation (Bai et al., 2003), but stabilizes protein levels of the CDK inhibitor $p27^{Kip1}$ through a non-transcriptional mechanism (Aoki et al., 2011). Transforming growth factor-β (TGF-β) induces G_1 arrest in normal cells by activating a transcriptional program that represses c-Myc and induces $p21^{WAF1/Cip1}$ and $p15^{Ink4B}$ (Siegel & Massagué, 2003). Many tumors are resistant to the anti-proliferative effect of TGFβ and this resistance has been attributed to TGF-β receptor or Smad4 mutations in several but not all types of tumors (Siegel & Massagué, 2003). One mechanism by which tumors that lack mutations in the TGF-β signaling pathway might become resistant to the anti-proliferative effect of TGF-β is through overexpression of the homeoprotein DLX4. DLX4 blocks the anti-proliferative effect of TGF-β in part by binding to Smad4 and preventing Smad4 from forming transcriptional complexes with Smad2 and Smad3 (Trinh et al., 2011). In addition, DLX4 impairs the DNA-binding ability of Sp1 and induces expression of c-Myc which in turn represses $p15^{Ink4B}$ and $p21^{WAF1/Cip1}$ transcription (Trinh et al., 2011). Intriguingly, *DLX2*, another *DLX* family member, counteracts the growth-inhibitory effect of TGF-β via different mechanisms. DLX2 acts as a transcriptional repressor of TGF-β type II receptor expression and promotes cell survival by inducing expression of betacellulin, a member of the epidermal growth factor family (Yilmaz et al., 2011).

3.3. Resistance to cell death

Cancer cells have evolved adaptive strategies to circumvent cell death programs that are triggered by physiological stresses (Hanahan & Weinberg, 2000). One selective advantage is the ability to survive as floating cells in body fluids. Ovarian cancer cells are often present in ascites as floating aggregates and this aggregation is thought to promote tumor cell survival (Lengyel, 2010). HOXA10 has been found to promote assembly of ovarian cancer cells into aggregates and to enable these cells to evade anoikis (Ko et al., 2010). Another selective advantage for tumor cells is the ability to evade cell death induced by chemotherapeutic agents. Down-regulation of the homeobox gene *BARX2* has been implicated in platinum-resistance of ovarian cancer cells (Sellar et al., 2002). HOXB7 has been reported to render breast cancer cells resistant to tamoxifen by transcriptional activation of epidermal growth factor receptor expression (Jin et al., 2012). Trinh et al (2013) recently identified that DLX4 induces expression of topoisomerase IIα (TOP2α), but decreases the sensitivity of tumor

cells to TOP2α-targeting drugs such as etoposide and doxorubicin by stimulating DNA repair and thereby reducing the level of drug-induced DNA damage. These two activities of DLX4 provided a possible explanation as to why some TOP2α-overexpressing tumors are not highly sensitive to drugs that target this enzyme. Together, these studies indicate that loss of expression or overexpression of specific homeobox genes in tumors might contribute to acquired chemoresistance, and that expression levels of these genes might potentially serve as predictors of responsiveness to therapy.

3.4. Replicative immortality

Whereas normal cells undergo only a limited number of cycles of cell division, cancer cells are capable of limitless replicative potential (Hanahan & Weinberg, 2000). Substantial evidence indicates the central role of telomeres in the capability for unlimited proliferation and that levels of telomerase, the specialized DNA polymerase which adds telomere repeat segments to the ends of telomeric DNA, are increased in tumor cells (Hanahan & Weinberg, 2011). The ability of homeobox genes to confer limitless replicative potential in solid tumors is not known. One possible negative regulator is *PITX1*. PITX1 has been described as having tumor-suppressive properties and represses transcription of the gene encoding telomerase reverse transcriptase that controls telomerase activity (Qi et al., 2011).

3.5. Angiogenesis

Angiogenesis is a well-established hallmark of cancer (Hanahan & Weinberg, 2000). Several homeoproteins have been identified to promote tumor growth and progression by inducing expression of pro-angiogenic growth factors [Figure 2]. DLX4 has been found to induce expression of vascular endothelial growth factor A (VEGF-A) and FGF-2 and to increase tumor microvessel density in mouse xenograft models of ovarian cancer (Hara et al., 2007). HOXB7 also induces VEGF-A and FGF-2 expression and stimulates angiogenesis in breast cancer and multiple myeloma (Caré et al., 2001; Storti et al., 2011). In addition, HOXB7 inhibits expression of the anti-angiogenic protein thrombospondin-2 (Storti et al., 2011). Overexpression of SIX1 in breast cancer has been found to promote lymphangiogenesis by inducing expression of VEGF-C (Wang et al., 2012a). Conversely, the ability of NKX3.1 to inhibit VEGF-C expression has been thought to be a mechanism by which loss of *NKX3.1* in prostate cancer leads to lymphangiogenesis (Zhang et al., 2008).

3.6. Invasion and metastasis

An extensively studied hallmark of cancer is the ability of tumor cells to invade adjacent tissues and colonize distant sites (Hanahan & Weinberg, 2000). A fundamental and initial step of this capability in carcinomas is the loss of epithelial features and acquisition of mesenchymal features. It is well-established that TGF-β promotes invasion and metastasis by inducing epithelial-to-mesenchymal transition (EMT) (Thiery et al., 2009). Several homeoproteins that are overexpressed in tumors, such as HOXB7 and SIX1, induce EMT and promote invasiveness (Wu et al., 2006; Micalizzi et al., 2010). Conversely, HOXA10 induces mesenchymal-to-epithelial transition and inhibits invasiveness, and its expression is silenced in high-grade endometrial carcinomas (Yoshida et al., 2006). EMT is orchestrated by a repertoire of transcription factors that are induced by TGF-β (Thiery et al., 2009).

These include the Snail, Twist and ZEB families of transcription factors. Several homeoproteins mediate their pro- or anti- metastatic effects through direct transcriptional regulation of genes that control the EMT program [Figure 2]. In prostate cancer cells, NKX3.1 represses *TWIST1* transcription (Eide et al., 2013). SIX1 induces EMT in breast cancer cells by activating transcription of the gene encoding the TGF-β type I receptor (Micalizzi et al., 2010). SIX1 also promotes metastasis of rhabdomyosarcoma by inducing expression of the cytoskeletal protein ezrin (Yu et al., 2006). The EMT program has been coupled to the acquisition of cancer stem cell (CSC) features (Mani et al., 2008). It is possible that homeobox genes that regulate EMT might also control CSC features. Other homeobox genes might control the self-renewal capability of CSCs. *Nanog* is a homeobox gene that promotes pluripotency of mouse embryonic stem cells (Mitsui et al., 2003) and has been also found to control 'stemness' of glioma stem cells (Zbinden et al., 2010).

4. Functional significance of homeobox genes in the emerging hallmarks and enabling characteristics of cancer

In recent years, two additional traits have emerged as important hallmarks of cancer (Hanahan & Weinberg, 2011). One involves the capability to deregulate cellular metabolism in order to support tumor growth. The second emerging hallmark is the capability of cancer cells to evade immune destruction. In addition, two characteristics have been described that facilitate the acquisition of both the established and emerging hallmarks of cancer (Hanahan & Weinberg, 2011). These enabling characteristics are the development of genomic instability and tumor-promoting inflammation. Although the mechanisms of many homeobox genes have not yet been precisely defined, recent studies have provided insight into how homeobox genes might control these emerging hallmarks of cancer and enabling characteristics.

4.1. Deregulated cellular metabolism

The control of the metabolic switch in cancer cells to glycolysis has been the focus of extensive investigation (Hanahan & Weinberg, 2011). To date, there is no conclusive evidence that deregulation of homeobox genes drives tumor growth by reprogramming energy metabolism. However, several studies have demonstrated the significance of specific homeobox genes in controlling glucose levels and responses to metabolic stress. Deficiency of *Sax2*, a homeobox gene that is predominantly expressed in the brainstem, has been found to decrease fat and glycogen storage and blood glucose levels (Simon et al., 2007). Expression of *DLX2* in tumor cells is induced by glucose deprivation and mediates metabolic stress-induced cell death (Lee et al., 2011). One important mechanism by which metabolism in cancer cells is reprogrammed is through increased expression of glucose transporters that increase glucose uptake (Hanahan & Weinberg, 2011). The gene encoding glucose transporter type 2 is a direct transcriptional target of PDX1, a homeoprotein that controls embryonic development of the pancreas and differentiation of insulin-producing islet β cells (Waeber et al., 1996).

4.2. Evasion of immune destruction and modulation of the tumor microenvironment

Tumor growth is controlled by dynamic interplay between tumor cells and a variety of cell types in the stroma such as fibroblasts, endothelial cells and immune cells (Tlsty & Coussens, 2006). In a recent study, Ko et al (2012) demonstrated that expression of HOXA9 in ovarian cancer cells induces normal peritoneal fibroblasts and mesenchymal stem cells (MSCs) to acquire features of CAFs that promoted growth of tumor and endothelial cells. This tumor-promoting effect of HOXA9 was attributed in substantial part to its transcriptional activation of the gene encoding TGF-β2. HOXA9-induced, tumor-derived TGF-β2 acted in a paracrine manner on peritoneal fibroblasts and MSCs and induced these cells to express mitogenic and pro-inflammatory growth factors (Ko et al., 2012). TGF-β ligands also inhibit proliferation and function of lymphocytes, and down-regulate major histocompatibility antigens on tumor cells (Li et al., 2006). An implication of the study of Ko *et* al (2012) is that aberrant expression of a homeoprotein can, through regulating expression of tumor-derived factors, promote an inflammatory microenvironment that is permissive for tumor growth and also potentially enables tumors to escape immune destruction.

4.3. DNA repair and genomic instability

Genomic instability endows cancer cells with genetic alterations that drive tumor progression and can stem from defects in components of the genome maintenance machinery that detect and repair DNA damage (Hanahan & Weinberg, 2011). One mechanism by which aberrantly expressed homeobox genes can potentially lead to genomic instability is through cell cycle checkpoint deregulation. SIX1 overexpression has been reported to lead to genomic instability in breast cancer cells by attenuating the DNA damage–induced G_2 cell cycle checkpoint via its induction of cyclin A1 expression (Coletta et al., 2008). Repair of DNA double-strand breaks (DSBs) by non-homologous end-joining (NHEJ) is error-prone and misrepair of DSBs can lead to genomic instability (Kasparek & Humphrey, 2011). The canonical NHEJ pathway is initiated by the binding of Ku heterodimers to DNA ends which then recruit other factors to form a complex that enables ligation of DNA ends with little or no homology (Kasparek & Humphrey, 2011). Recent studies have revealed intriguing non-transcriptional functions of several homeoproteins in repairing DSBs. CDX2, HOXB7 and DLX4 have been reported to interact with Ku proteins but have strikingly different effects. CDX2, which is often down-regulated in colon cancer cells, has been found to inhibit end-joining activity (Renouf et al., 2012). In contrast, HOXB7 and DLX4, which are overexpressed in breast and ovarian cancers, stimulate end-joining activity (Rubin et al., 2007; Trinh et al., 2013). Furthermore, Trinh et al (2013) found that DLX4 increases both the frequency and magnitude of erroneous end-joining. Because NHEJ depends on DNA ends being held in close alignment in order for end-processing and ligation to occur, it is possible that the interaction of DLX4 with Ku proteins increases erroneous repair by altering the alignment of DNA ends.

5. Clinical implications and future directions

In summary, increasing evidence indicates the functional significance of overexpression or loss of expression of distinct sets of homeobox genes in the hallmarks and enabling

characteristics of cancer [Figure 2]. However, it is not clear whether and how a given homeobox gene controls an acquired capability or enabling characteristic in a tissue-specific manner or in cells of different lineages. For example, HOXB7 has tumor-promoting properties in several different types of tumors (Caré et al., 1996; Caré et al., 1998; Naora et al., 2001; Storti et al., 2011). On the other hand, HOXA9 has tumor-promoting properties in ovarian cancer (Ko et al., 2012), but has tumor-suppressive properties in breast cancer (Reynolds et al., 2006). The mechanisms that cause aberrant expression of homeobox genes in solid tumors also require further investigation. Despite their functional significance, homeoproteins do not represent ideal therapeutic targets that can be readily inhibited with high specificity as these proteins are transcription factors that share tracts of homology with other family members. On the other hand, further study of the mechanisms of homeoproteins, their transcriptional targets and other downstream effectors could provide important insights into focal points for therapeutic intervention. In addition, recent studies have demonstrated the importance of several homeobox genes in chemoresistance and raise the possibility that expression levels of these genes could serve as predictors of responsiveness to therapy. Because homeobox genes play essential functions in lineage-specification, their expression patterns in tumors could also provide valuable information for differential diagnosis when used in the appropriate clinical settings.

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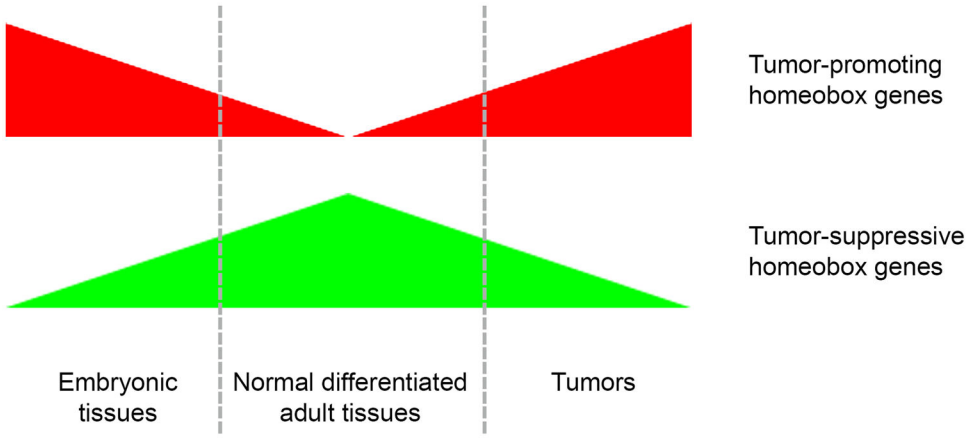

Figure 1. Trends in relationships between expression patterns and functional significance of homeobox genes in tumors

Homeobox genes that are expressed in embryonic tissues and are 'reactivated' in tumors (red) tend to have tumor-promoting properties. Homeobox genes whose expression is normally maintained in differentiated adult tissues but is down-regulated in tumors (green) often exhibit tumor-suppressive properties.

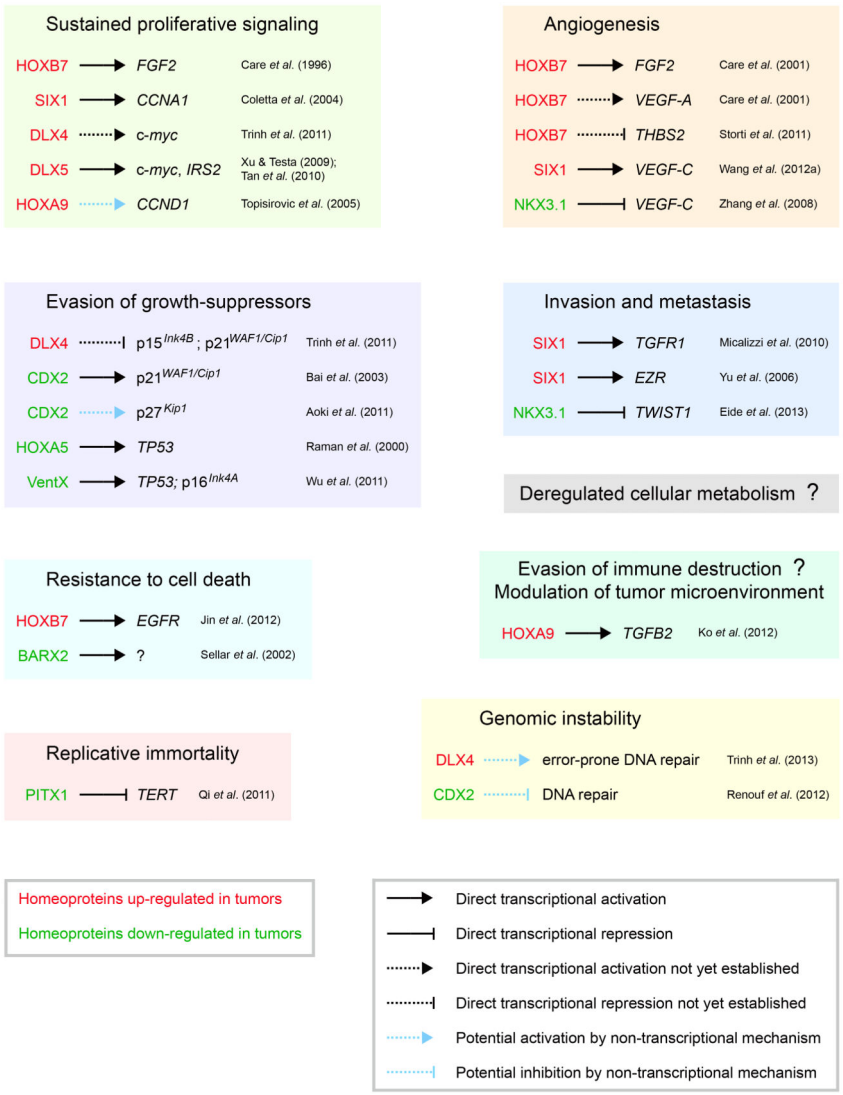

Figure 2. Mechanisms of aberrant homeobox gene expression in the hallmarks of cancer and enabling characteristics

Examples of homeoproteins that are up- or down-regulated in tumors, their functional significance, transcriptional targets and effector genes.

Table I

Examples of chromosomal aberrations in homeobox gene-containing loci in solid tumors

Homeobox gene	Chromosomal region	Lesion/Tumor type	References
LOH			
NKX3.1	8p21	PIN, Prostate cancers	Emmert-Buck *et al.* (1995); He *et al.* (1997)
BARX2	11q24-q25	Ovarian cancers	Gabra *et al.* (1996)
CUTL1	7q22	Uterine leiomyomas	Zeng *et al.* (1997)
LAGY (HOPX)	4q11-13.1	Lung cancers	Chen *et al.* (2003)
Gene Amplification			
HOXB7	17q21.3-q22	Breast, ovarian cancers	Wu *et al.* (2006); Naora *et al.* (2001)
DLX4 (BP1)	17q21.3-q22	Breast, ovarian cancers	Man *et al.* (2005), Hara *et al.* (2007)

Table II

Examples of tumor-suppressive homeobox genes that are methylated in solid tumors

Homeobox gene	Tumor type	References
HOXA5	breast	Raman *et al.* (2000)
HOXA9	breast	Reynolds *et al.* (2006)
HOXA10	endometrial	Yoshida *et al.* (2006)
HOXD10	gastric	Wang *et al.* (2012b)
CDX2	colorectal	Kawai *et al.* (2005)