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Homeobox Genes and Their Functional Significance in Ovarian Tumorigenesis

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1. Introduction

It is widely recognized that many pathways that control normal embryonic patterning are deregulated in human cancers. Mutations or aberrant expression of components of the Wnt, Hedgehog and Notch signaling pathways have been demonstrated to play pivotal roles in tumorigenesis. Homeobox genes constitute an evolutionarily conserved gene super-family that represents another important class of patterning regulators. These genes encode transcription factors that are essential for controlling cell differentiation and specification of the body plan during embryonic development. Although many homeobox genes have been reported to be aberrantly expressed in ovarian cancer, the functional significance of these genes in ovarian tumorigenesis has only emerged in recent years. This chapter discusses recent research studies that demonstrate that homeobox genes have diverse functions in the biology of ovarian cancer. These functions include specifying patterns of histologic differentiation of ovarian cancers, controlling growth and survival of tumor cells, and promoting tumor angiogenesis, cell-cell interactions and tumor cell invasiveness. This chapter discusses how studies of homeobox genes provide insights into our understanding of the cell-of-origin of ovarian cancers, the striking morphologic heterogeneity of these tumors, and the unique clinical behavior of ovarian cancer.

2. Overview of homeobox genes

Homeobox genes were first discovered in *Drosophila* by their mutations that caused homeotic transformation, a phenomenon in which body segments form in inappropriate locations (Gehring & Hiromi, 1986; McGinnis & Krumlauf, 1992). A classic example of a homeotic transformation in *Drosophila* is the formation of legs rather than antennae caused by ectopic expression of the *Antennapedia* gene (Schneuwly et al., 1987). Homeobox genes play essential roles in defining the unique identities of specific organs and body regions during embryonic development. Distinct sets of homeobox genes control skeletal patterning, limb formation, craniofacial morphogenesis, development of the central nervous system and other organ systems including the gastrointestinal tract and urogenital organs (Capecchi, 1997; Beck, 2002; Panganiban & Rubenstein, 2002; Christensen et al., 2008). Homeobox genes also control cell renewal and tissue regeneration processes in adults such as hematopoiesis, angiogenesis, spermatogenesis and endometrial remodeling (Gorski & Walsh, 2000; Argiropoulos & Humphries, 2007; Vitiello et al., 2007; Maclean & Wilkinson, 2010).

Mutations in homeobox genes cause a spectrum of complex developmental disorders. For example, mutations in the *HOXA13* gene cause hand-foot-genital syndrome, an autosomal dominant trait characterized by distal limb and genitourinary malformations (Mortlock & Innis, 1997). *SIX1* mutations cause branchio-oto-renal syndrome, a disorder characterized by hearing loss and renal abnormalities (Ruf et al., 2004).

2.1 Organization of mammalian homeobox genes

There are approximately 200 homeobox genes in the human genome (Tupler et al., 2001) and these are categorized into several different families named after their homologs in the fly (Banerjee-Basu & Baxevanis, 2001). For example, members of the mammalian *PAX, MSX* and *CDX* gene families are related to the *Drosophila* genes *paired*, *muscle segment* and *caudal,* respectively. Whereas most homeobox genes are scattered throughout the genome, the members of the mammalian *HOX* and *DLX* gene families are organized in clusters. The *HOX* family is related to the *Drosophila HOM-C* cluster and comprises 39 genes. *HOX* genes are organized in four clusters located on different chromosomes and are aligned into 13 paralogous groups (Figure 1). The six members of the *DLX* family are related to the *Drosophila distal-less* (*dll*) gene and are organized in bigene clusters located upstream of *HOX* clusters (Figure 1). These gene clusters are thought to have arisen from gene duplication during evolution (Sumiyama et al., 2003; Lemons & McGinnis, 2006). A striking feature of *HOX* genes is their temporal and spatial colinearity. This phenomenon describes the coupling of the timing and location of expression of *HOX* genes along the anterior-posterior body axis to their relative position in the gene clusters. *HOX* genes that are located at the 3′ end of the clusters tend to be expressed early in development and in anterior body regions, whereas those at the 5′ end of clusters are generally expressed later and in more posterior body regions (McGinnis & Krumlauf, 1992; Pearson et al., 2005) (Figure 1).

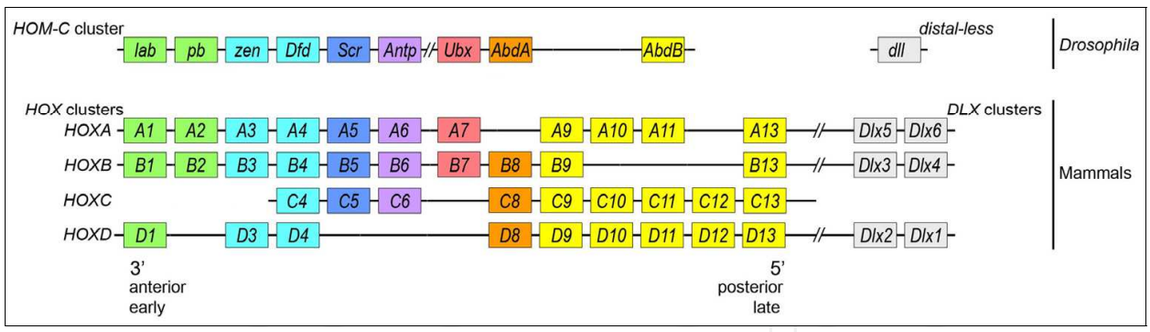


Fig. 1. Organization of *HOX* and *DLX* gene clusters in *Drosophila* and mammals.

2.2 Structural features and mechanisms

Homeobox genes encode transcription factors, often called 'homeoproteins' that are characterized by a 61 amino acid DNA-binding domain termed the homeodomain. The homeodomain forms a helix-turn-helix structure that binds DNA elements containing a TAAT core motif (Gehring et al., 1994). Although the three-dimensional structure of the homeodomain is highly conserved among homeoproteins, diversity in the amino acid residues gives rise to different DNA-binding specificities (Gehring et al., 1994; Biggin & McGinnis, 1997). Binding affinity and selectivity of homeoproteins for target gene promoters

are also mediated by additional conserved motifs that are present in the different families. PAX proteins contain an additional DNA-binding domain called the paired box (Robson et al., 2006). HOX proteins contain a hexapeptide motif that mediates interactions with PBX co-factors (Chang et al., 1995). MEIS proteins also act as co-factors for HOX proteins (Shanmugam et al., 1999). Furthermore, target specificity and functional diversity of homeoproteins are achieved via interactions with other transcription factors (Chariot et al., 1999). Whereas homeoproteins have highly selective functions *in vivo*, they exhibit relatively promiscuous DNA-binding *in vitro* (Biggin & McGinnis, 1997). As a consequence, only few *bona fide* target genes have been identified. Several homeoproteins also have intriguing non-transcriptional functions. The *Drosophila* homeoprotein Bicoid represses translation of *caudal* mRNA by directly binding to the 3' untranslated region of *caudal* mRNA (Dubnau & Struhl, 1996). HOXA9 has been reported to bind the translation initiation factor eIF4E and to stimulate eIF4E-dependent export of *cyclin D1* mRNA (Topisirovic et al., 2005). HOXB7 binds Ku proteins and stimulates DNA repair (Rubin et al., 2007).

2.3 Misexpression of homeobox genes in tumors

In the past 15 years, there has been increasing evidence that many homeobox genes are aberrantly expressed in a variety of malignancies. Much of the pioneering work has come from the hematopoietic field, where overexpression of various *HOX* genes has been found to promote leukemogenesis (Thorsteinsdottir et al., 1997; Kroon et al., 1998; Fischbach et al., 2005). Expression patterns of homeobox genes in solid tumors can be divided into three broad categories (Abate-Shen, 2002; Samuel & Naora, 2005). Firstly, homeobox genes that are normally expressed in differentiated adult tissues are often down-regulated in tumors. Two examples are *NKX3.1* and *HOXA10* that control morphogenesis of the prostate and uterus respectively, and are expressed in these tissues during development and in the adult (Bhatia-Gaur et al., 1999; Benson et al., 1996). *NKX3.1* is frequently deleted in prostate cancers (He et al., 1997), whereas *HOXA10* is often silenced by methylation in high-grade endometrial cancers (Yoshida et al., 2006). Secondly, homeobox genes can be re-expressed in tumors derived from tissues in which these genes are normally expressed during embryonic development. *PAX2,* a regulator of urogenital patterning, is normally expressed in the developing kidney and is reactivated in renal cancers (Dressler et al., 1990; Gnarra & Dressler, 1995). A third, less common, category includes homeobox genes that are expressed in tumors derived from a lineage in which the particular gene is not expressed during development. An example is *PAX5* that is expressed in medulloblastoma but not in neonatal cerebellum (Kozmik et al., 1995). Loss or gain of homeobox gene expression in tumors therefore often reflects an inappropriate recapitulation of embryonic pathways and, in many but not all cases, this misexpression can be indicative of the cell-of-origin of the tumor.

3. Homeobox genes and the origin of ovarian cancers

Whereas other types of tumors often exhibit 'loss' of the specialized features of the tissue from which they derive, many ovarian cancers exhibit specialized features of non-ovarian lineages. Epithelial ovarian cancers have been thought to originate from the simple monolayered epithelium that lines the ovarian surface (OSE) or from post-ovulatory inclusion cysts that arise from invaginations of the ovarian surface (Feeley & Wells, 2001). However, the major subtypes of ovarian cancer (serous, endometrioid, mucinous) exhibit

morphologic features that resemble those of the epithelia of the reproductive tract that derive from the Müllerian ducts (*viz.* fallopian tube, endometrium, endocervix, respectively). Mucinous ovarian cancers also exhibit intestinal-like features. The OSE origin has been supported by several mouse genetic models in which tumors were induced by introducing specific oncogenic alterations into the OSE (Orsulic et al., 2002; Connolly et al., 2003; Wu et al., 2007). On the other hand, various histopathologic and genetic studies have supported origins in primary Müllerian derivatives such as the tubal fimbria (Lee et al., 2007) and in secondary Müllerian structures such as endometriosis (Prowse et al., 2006). Detailed discussions of these studies are beyond the scope of this chapter and these are elegantly reviewed in several articles (Dubeau, 2008; Jarboe et al., 2008; Cho & Shih, 2009).

3.1 *HOX* genes and the Müllerian phenotype

One argument against the OSE as the origin of ovarian cancers has been the lack of evidence that demonstrates the capability of OSE cells to differentiate along multiple Müllerian lineages. Differentiation of the Müllerian ducts is controlled by several sets of homeobox genes. These include the tandemly arranged *Hoxa9, Hoxa10, Hoxa11* and *Hoxa13* genes that are related to the *Drosophila* abdominal patterning gene *Abdominal-B* (*AbdB*) (Benson et al., 1996; Hsieh-Li et al., 1995; Zhao & Potter, 2001) (Figure 1). Targeted mutagenesis of *AbdB HOX* genes results in region-specific defects along the reproductive tract. For example, *Hoxa10*-deficient female mice exhibit homeotic transformation of the anterior segment of the uterus into oviductal-like structures (Benson et al., 1996). Replacement of the homeobox of the *Hoxa11* gene with that of *Hoxa13* in mice causes homeotic transformation of the uterus into cervical/vaginal-like structures (Zhao & Potter, 2001). The *AbdB HOX* genes are uniformly expressed along the axis of the Müllerian ducts early in embryonic development. As the ducts differentiate, *Hoxa9, Hoxa10, Hoxa11* and *Hoxa13* become expressed in the primordia of the fallopian tubes, uterus, lower uterine segment/cervix, and upper vagina, respectively (Taylor et al., 1997). This colinear *HOX* expression is maintained in the adult tract with sharply defined anterior boundaries of expression and tapered posterior expression. We have found that the *AbdB HOX* genes are not expressed in normal human OSE whereas their colinear expression patterns in Müllerian epithelia are recapitulated in the major subtypes of ovarian cancers according to the pattern of Müllerian-like differentiation of these tumors (Cheng et al., 2005). HOXA9 was found to be expressed in serous tumors and also in endometrioid and mucinous tumors. In contrast, HOXA10 was strongly expressed in endometrioid and mucinous but not serous tumors, whereas HOXA11 was mostly restricted to mucinous tumors (Table 1). Clear-cell ovarian carcinomas have features that overlap with those of serous and endometrioid tumors, and were found to express HOXA9 and HOXA10. This recapitulation of the *AbdB HOX* gene program in ovarian cancers could be interpreted to reflect Müllerian origins. However, by ectopically expressing *AbdB HOX* genes in undifferentiated, transformed mouse OSE cells and propagating transfected cells in the peritoneum of female mice, we demonstrated that OSE-derived cells acquire features of different Müllerian lineages. Mouse OSE cells that expressed *Hoxa9* formed papillary tumors that resembled high-grade serous ovarian carcinoma, whereas expression of *Hoxa10* and *Hoxa11* induced formation of high-grade endometrioid-like and mucinous-like tumors, respectively (Cheng et al., 2005). We also found that the *Hoxa7* gene, located 3′ of *Hoxa9*, is expressed in normal Müllerian epithelia and in differentiated ovarian tumors irrespective of their histologic subtype. Expression of

Hoxa7 in transformed mouse OSE cells promoted the abilities of *Hoxa9, Hoxa10* and *Hoxa11* to induce tumor differentiation along their respective pathways (Cheng et al., 2005).

The study of Cheng *et al* (2005) cannot be interpreted to conclusively demonstrate that the OSE is the cell-of-origin of ovarian cancers. However, the findings of this study suggest an intriguing model in which OSE-derived tumors acquire Müllerian phenotypes through homeotic transformation. The finding that colinearity of *AbdB HOX* expression (i.e. HOXA9, HOXA10, HOXA11) is recapitulated in ovarian cancers is striking, as it might explain the relative abundance of the ovarian cancer subtypes (i.e. serous> endometrioid> mucinous). The capability of OSE cells to acquire features of different lineages could stem from the intrinsically 'uncommitted' or embryonic-like phenotype of adult OSE cells (Auersperg et al., 2001; Naora, 2007). Unlike most other adult epithelia, the OSE lacks specialized features and expresses little or no E-cadherin (Maines-Bandiera & Auersperg, 1997). The OSE expresses both fibroblast markers and markers characteristic of simple epithelium (Auersperg et al., 1994), and also highly expresses stem cell maintenance genes (Bowen et al., 2009). This plasticity of the OSE is likely to be important for post-ovulatory repair (Auersperg et al., 2001). Both the OSE and Müllerian ducts derive from the coelomic epithelium, and the predominance of Müllerian phenotypes in ovarian cancers could reflect the close primordial relationship between the OSE and Müllerian ducts (Auersperg et al., 2001). More recently, it has been reported that the OSE and tubal fimbria are anatomically contiguous and that these tissues are parts of a transitional epithelium (Auersperg, 2011). On the other hand, less common subtypes of ovarian cancers such as clear-cell and transitional-cell tumors have features resembling those of renal and urothelial tissues whose embryonic relationship to the OSE is more distant.

3.2 PAX expression and differential diagnosis

More recently, expression of other homeobox genes that control urogenital patterning has been studied in ovarian cancers. *Pax2* is expressed in the developing kidneys, Wolffian ducts and Müllerian ducts (Dressler et al., 1990; Torres et al., 1995). *Pax8* is also expressed in the developing kidney and Müllerian ducts (Plachov et al., 1990). Female *Pax2* homozygous mutant mice lack the entire reproductive tract (Torres et al., 1995). Female *Pax8* null mice do not develop a functional uterus whereas development of the oviduct, cervix and vagina is unaffected (Mittag et al., 2007). PAX2 and PAX8 are normally expressed in tubal, endometrial and endocervical epithelia (Tong et al., 2007; Tong et al., 2011). PAX2 has also been detected in secondary Müllerian structures such as endometriosis, endosalpingiosis and rete ovarii (Tong et al., 2007). PAX2 and PAX8 have been detected in 64 to 100% of non-mucinous ovarian cancers, and in 74 to 90% of primary and metastatic renal cell carcinomas (Bowen et al., 2007; Tong et al., 2007; Nonaka et al., 2008; Chivukula et al., 2009; Zhai et al., 2010; Laury et al., 2011; Tacha et al., 2011). The absence or rareness of PAX2 and PAX8 in many other types of cancers such as colorectal carcinomas and mesotheliomas has raised the possibility that these proteins could be useful markers for differential diagnosis (Tong et al., 2007; Zhai et al., 2010; Laury et al., 2011; Tacha et al., 2011), but this depends on the appropriate setting. Ovarian metastasis from renal cell carcinoma and renal metastasis from ovarian carcinoma are rare. However, ovarian cancer commonly involves the uterus and omentum. PAX2 and PAX8 are frequently expressed in endometrial carcinomas (56 to 98%) (Sharma et al., 2010; Laury et al., 2011; Tacha et al., 2011), but have been detected at low frequency (<10%) in mucinous ovarian cancers that closely resemble colorectal carcinomas (Muratovska et al., 2003; Bowen et al., 2007; Nonaka et al., 2008). On the other hand, PAX8

has been reported to have comparable sensitivity to the Wilms tumor gene product WT1 in detecting serous ovarian cancer cells in fluid cytologic specimens and superior specificity to WT1 in distinguishing tumor cells from mesothelial cells (McKnight et al., 2010).
One interpretation of the frequency of PAX2 and PAX8 expression in ovarian cancers is that it implicates Müllerian origins of these tumors (Tong et al., 2007; Tong et al., 2011). However, there are several observations that challenge this notion. Whereas most studies have not detected PAX2 or PAX8 in normal OSE, these proteins have been detected in inclusion cysts (Bowen et al., 2007; Chivukula et al., 2009; Zhai et al., 2010; Auersperg, 2011). PAX8 has also been detected in peritoneal serous carcinomas (Tong et al., 2011). These tumors originate from the peritoneal mesothelium, a coelomic epithelial derivative to which the OSE is very closely related. Furthermore, PAX2 and PAX8 have been detected in tumors derived from non-urogenital lineages such as Kaposi's sarcoma (Buttiglieri et al., 2004) and thymic tumors (Laury et al., 2011). These cases might fall within the third category of anomalously expressed homeobox genes described above.

3.3 *CDX2* and the intestinal phenotype

Another homeoprotein that has been extensively studied in differential diagnosis is CDX2. *Cdx2* controls intestinal differentiation and is expressed in the gut during development and in the adult (James et al., 1994). In contrast to PAX2 and PAX8, CDX2 is more frequently detected in mucinous ovarian carcinomas (64 to 93%) than in non-mucinous subtypes (0 to 7%) (Fraggetta et al., 2003; Werling et al., 2003; Groisman et al., 2004). CDX2 has been detected at lower frequency in mucinous ovarian cystadenomas and borderline tumors in keeping with the decreased prevalence of intestinal differentiation in these tumors (Werling et al., 2003). The most common secondary tumor to mimic an ovarian primary tumor is metastatic colorectal adenocarcinoma. Distinguishing primary mucinous ovarian carcinoma from metastatic colorectal adenocarcinoma is essential for clinical management but can be very difficult given their similar morphologic features. CDX2 alone is unsuitable for distinguishing primary from secondary mucinous ovarian tumors, as it is expressed in 90% of colorectal carcinomas metastatic to the ovary (Tornillo et al., 2004). However, several studies have reported promising predictive values when CDX2 is combined with other markers. These include cytokeratin 7 and mucin 5AC that are more frequently expressed in cancers of ovarian rather than lower gastrointestinal origin, and mucin 2 and carcinoembryonic antigen that are more frequently expressed in cancers of gastrointestinal rather than ovarian origin (Groisman et al., 2004; Park et al., 2007).

3.4 Other diagnostic applications of homeoproteins

The studies discussed above indicate that expression of several homeobox genes in ovarian cancers is associated with specific patterns of differentiation (Table 1), and raise the possibility that homeoproteins could serve as markers for differential diagnosis when used in appropriate settings and in combination with other tissue-specific markers. Misexpressed homeoproteins might also be useful for early detection. A significant limitation of assaying molecules that are shed by tumor cells is that their levels might not be detected in body fluids particularly when tumors are small. On the other hand, cancer patients often generate antibodies to molecules that are expressed in tumors and not in normal tissues and to self-antigens that are overexpressed in tumors. These circulating antibodies can be regarded as 'signals' that are amplified by the immune system and could serve as biomarkers for early cancer detection. One approach of identifying tumor antigens is to screen tumor cDNA

expression libraries with cancer patient sera and has been termed SEREX (serologic identification of antigens by recombinant expression cloning) (Sahin et al., 1995). We have identified the HOXA7 and HOXB7 homeoproteins as ovarian tumor antigens by using the SEREX approach (Naora et al., 2001a, 2001b). Serum antibodies to HOXA7 were detected in 16 of 24 (67%) patients with differentiated ovarian carcinomas and in 0/30 (0%) healthy women (Naora et al., 2001a). Antibodies to HOXA7 were also detected in 13 of 19 (68%) women with cystadenomas, but in only one of 24 (4%) patients with poorly differentiated ovarian carcinoma (Naora et al., 2001a). This serologic reactivity reflected the prevalence of HOXA7 expression in cystadenomas and differentiated ovarian carcinomas as compared to poorly differentiated carcinomas (Naora et al., 2001a). Whereas HOXA7 is absent from normal OSE, HOXB7 was detected in normal OSE and at higher levels in ovarian carcinomas irrespective of the type or degree of differentiation (Naora et al., 2001b). Serum antibodies to HOXB7 were detected in only one of 29 (3%) healthy women and in 13 of 39 (33%) ovarian cancer patients (Naora et al., 2001b). Although this frequency is not high, the application of Bayesian modeling to multiplexed assays of serum antibodies to multiple ovarian tumor antigens has found that assaying serum antibodies to HOXB7, p53 and the antigen NY-CO-8 is the most effective combination for discriminating between ovarian cancer patients and healthy women (Erkanli et al., 2006). Widschwendter *et al.* (2009) reported that methylation of the *HOXA9* and *HOXA11* genes in normal endometrium can discriminate between premenopausal women with ovarian cancer and age-matched healthy women. Although the biological significance of these findings is unclear, this study raises the intriguing possibility that the methylation status of specific *HOX* genes in the endometrium might be useful for predicting risk of ovarian cancer.

	HOXA7*	HOXA9	HOXA10	HOXA11	PAX2	PAX8	CDX2
serous	+	+	-	-	+	+	-
endometrioid	+	+	+	-/+	-	+	-
mucinous	+	+	+	+	-	-/+	+
clear-cell	+	+	+	-	+	+	?

(* mostly restricted to differentiated tumors)

Table 1. Homeobox gene expression in histologic subtypes of ovarian cancer.

4. Homeobox genes and the hallmarks of cancer

Given their essential developmental functions, it is not surprising that many homeobox genes are misexpressed in different types of cancers. In some cases, this aberrant expression reflects changes in cell differentiation in tumors and could occur as a consequence of tumorigenesis. On the other hand, there is increasing evidence that anomalous expression of homeobox genes plays causal roles in tumorigenesis (Abate-Shen, 2002; Samuel & Naora, 2005; Robson et al., 2006). Overexpression of several *HOX* genes in bone marrow cells leads to acute myeloid leukemia (Thorsteinsdottir et al., 1997; Kroon et al., 1998; Fischbach et al., 2005). Conversely, loss or down-regulation of a homeobox gene that is normally expressed in adult tissues can predispose cells for transformation. Inactivation of *Nkx3.1* in mice leads to the development of lesions that resemble prostate intraepithelial neoplasia (Kim et al.,

2002a). Inactivation of *Nkx3.1* cooperates with loss-of-function of *Pten* to induce carcinoma (Kim et al., 2002b). *Cdx2* heterozygous mutant mice develop adenomatous intestinal polyps (Chawengsaksophak et al., 1997). *Cdx2* inactivation enhances the sensitivity of mice to chemically induced colon carcinogenesis (Bonhomme et al., 2003). Re-expression of *Nkx3.1* and *Cdx2* in prostate and colon cancer cells, respectively, inhibits cell proliferation (Kim et al., 2002a; Mallo et al., 1998). On the other hand, re-expression of *Hoxa10* in endometrial cancer cells does not alter proliferation but inhibits invasive behavior (Yoshida et al., 2006). Up- or down- regulation of homeobox genes in tumors, depending on their context, can therefore significantly modulate different hallmark capabilities of cancer.

4.1 Sustained proliferative signaling

A well-established hallmark of cancer cells is their ability to sustain chronic proliferation (Hanahan and Weinberg, 2000). One important growth factor that promotes autocrine cell growth and that is frequently overexpressed in ovarian cancers is fibroblast growth factor-2 (FGF-2) (Le Page et al., 2006). The *FGF-2* gene is a transcriptional target of HOXB7 (Caré et al., 1996). Enforced expression of *HOXB7* in OSE cells induces FGF-2 expression and cell proliferation (Naora et al., 2001b). The homeoprotein DLX4 is absent from most normal adult tissues and is expressed in >50% of ovarian cancers (Hara et al., 2007). We have found that overexpression of DLX4 in ovarian cancer cells induces FGF-2 expression, increases clonogenicity *in vitro* and promotes tumor growth *in vivo* (Hara et al., 2007), but it is not known whether DLX4 directly activates *FGF-2* transcription. We recently found that DLX4 also induces expression of c-Myc (Trinh et al., 2011). This induction occurs by two mechanisms. We identified that DLX4 prevents transforming growth factor-β (TGF-β)-mediated repression of c-*myc* transcription, and also induces c-*myc* promoter activity independently of TGF-β/Smad signaling (Trinh et al., 2011). DLX5, another member of the *DLX* family, has also been found to directly activate c-*myc* transcription in lung cancer cells (Xu and Testa, 2009). It has been reported that DLX5 is overexpressed in ovarian cancers and that inhibiting DLX5 expression by RNA interference attenuates AKT signaling and inhibits growth of ovarian cancer cells (Tan et al., 2010). Furthermore, *DLX5* cooperates with activated *HRAS* in transformation of human OSE cells. This growth-stimulatory effect of DLX5 has been attributed in part to its ability to activate transcription of the gene encoding insulin receptor substrate 2, an oncogenic signaling adaptor protein (Tan et al., 2010).

The studies discussed above demonstrate that activation of specific sets of homeobox genes in ovarian cancers drives tumor cell proliferation by inducing transcription of genes that encode multiple, different components of signaling pathways. In several cases, a homeobox gene promotes proliferation by the same mechanism in cells of different lineages. HOXB7 induces FGF-2 expression in OSE cells, breast cancers and melanomas, and stimulates growth of these cell types (Caré et al., 1996; 1998; Naora et al., 2001b). Overexpression of *SIX1* stimulates proliferation of breast and ovarian cancer cells by inducing cyclin A1 expression (Coletta et al., 2004; Behbakht et al., 2007). On the other hand, the effect of a homeobox gene can be cell type-specific. For example, overexpression of HOXA10 in myelomonocytic cells activates transcription of the gene encoding the cyclin-dependent kinase inhibitor $p21^{WAF1/Cip1}$ and induces cell cycle arrest in G_1 phase (Bromleigh & Freedman, 2000). In contrast, we have found that overexpression of HOXA10 in OSE-derived cells has no effect on cell proliferation (Ko et al., 2010). Because homeoproteins of a given family share regions of extensive homology, it is not surprising that family members

have overlapping functions. For example, both DLX4 and DLX5 induce c-Myc expression (Xu and Testa 2009; Trinh et al., 2011). On the other hand, MSX1 induces expression of growth arrest genes such as GADD153 and inhibits proliferation of ovarian cancer cells (Park et al., 2001), whereas MSX2 promotes ovarian cancer growth (Zhai et al., 2011). As discussed earlier, diversity in amino acid residues in the homeodomain and other motifs of family members gives rise to different DNA-binding specificities and can result in different phenotypes. The function or mechanism of a homeoprotein cannot therefore be inferred from studies of its related family members.

4.2 Evasion of growth-suppressors

A second important hallmark of cancer cells is their ability to circumvent signals that inhibit cell growth (Hanahan & Weinberg, 2000). Whereas TGF-β induces G_1 arrest in most types of normal cells, many tumors are resistant to the anti-proliferative effect of TGF-β (Siegel & Massagué, 2003). The gene responses that are central to the TGF-β cytostatic program are activation of the cyclin-dependent kinase inhibitors $p15^{Ink4B}$ and $p21^{WAF1/Cip1}$ and repression of c-myc and ID transcription factors. This cytostatic program is tightly regulated by a network of transcription factors that include Smad proteins, Sp1 and c-myc (Feng et al., 2000; 2002; Gartel et al., 2001). Resistance to the anti-proliferative effect of TGF-β has been attributed to TGF-β receptor or Smad4 mutations in several types of tumors, particularly those of gastrointestinal origin (Markowitz et al., 1995; Hahn et al., 1996). TGF-β receptor mutations have been detected in 12 to 31% of ovarian cancers, but many TGF-β-resistant ovarian cancers have been found to express functional receptors and rarely have Smad4 mutations (Yamada et al., 1999; Wang et al., 2000; Francis-Thickpenny et al., 2001). We have found that DLX4 blocks the anti-proliferative effect of TGF-β by inactivating transcriptional control of the TGF-β cytostatic program through three distinct but integrated mechanisms (Trinh et al., 2011). Firstly, DLX4 directly binds Smad4 and prevents Smad4 from forming transcriptional complexes with Smad2 and Smad3. Secondly, DLX4 binds the DNA-binding domain of Sp1 and impairs the DNA-binding ability of Sp1. In addition, DLX4 induces expression of c-Myc, a repressor of $p15^{Ink4B}$ and $p21^{WAF1/Cip1}$ transcription (Trinh et al., 2011). An important outcome of our finding that DLX4 disables key transcriptional control mechanisms of the TGF-β cytostatic program is that it explains why tumors that lack TGF-β receptor or Smad mutations become resistant to the anti-proliferative effect of TGF-β.

4.3 Resistance to cell death

Cancer cells encounter many physiologic stresses that trigger cell death and have evolved adaptive strategies to circumvent cell death programs. One important selective advantage is evasion of anoikis. A significant proportion of ovarian cancer cells in ascites exist as multicellular aggregates (Burleson et al., 2004). We have found that overexpression of HOXA10 in OSE-derived cells promotes homophilic cell adhesion and enables these cells to escape anoikis (Ko et al., 2010). Another selective advantage is the ability to survive under conditions where levels of growth factors are limited. We have found that DLX4 enables ovarian cancer cells to escape apoptosis induced by withdrawal of exogenous growth factors. This effect was due at least in part to induction of FGF-2 expression by DLX4 in tumor cells (Hara et al., 2007). In addition, DLX4 (also known as BP1 and DLX7) has been reported to induce bcl-2 and GATA-1 expression and to promote survival of leukemic and

breast cancer cells (Shimamoto et al., 1997; Stevenson et al., 2007). PAX2 has also been reported to promote survival of ovarian cancer cells and various other cell types such as bladder cancer cells, Kaposi's sarcoma and renal cell carcinoma cells (Gnarra & Dressler, 1995; Muratovska et al., 2003; Buttiglieri et al., 2004), but the underlying mechanism of the anti-apoptotic effect of PAX2 is not known.

Chemoresistance is a major challenge in the clinical management of ovarian cancer. *BARX2* is a homeobox gene that has been strongly implicated in modulating sensitivity of tumor cells to platinum. A study by Sellar *et al.* (2002) investigated isogenic ovarian cancer cell lines that were established from patients' tumors before and after platinum therapy. It was found that *BARX2* expression was down-regulated in tumor cell lines that were established upon tumor recurrence after platinum therapy and that transfection of *BARX2* into platinum-resistant cells reversed platinum-resistance. There has been significant interest in studying platinum-resistance in stem cell-like cell populations in ovarian cancers, and the homeoprotein Nanog has been used as a stem cell marker in these studies (Zhang et al., 2008). Furthermore, some homeobox genes confer resistance to cell death induced by other agents or signals. Expression of *HOXB13* in ovarian cancer cells has been reported to confer resistance to tamoxifen-mediated apoptosis (Miao et al., 2007). On the other hand, *SIX1* overexpression renders ovarian cancer cells resistant to tumor necrosis factor-related apoptosis inducing ligand (TRAIL)-mediated apoptosis (Behbakht et al., 2007).

4.4 DNA repair and genomic instability

Most agents that are commonly used to treat ovarian cancer induce cell death by causing DNA damage. The DNA double-strand break (DSB) is the most dangerous type of DNA damage. DSBs are induced by ionizing radiation and topoisomerase II inhibitors such as etoposide (Helleday et al., 2008). The inability of a cell to properly respond to DSBs leads to genomic instability. Genomic instability has been described as an 'enabling' characteristic of cancer cells (Hanahan & Weinberg, 2011). The primary mechanisms that repair DSBs are homologous recombination (HR) and non-homologous end-joining (NHEJ). The latter is the dominant DSB repair pathway in mammalian cells and is error-prone (Lieber et al., 2003). Both deficiencies and increases in NHEJ activity contribute to DNA repair infidelity and genomic instability (Difilippantonio et al., 2000; Brady et al., 2003). Several homeoproteins have been implicated in DNA repair and genomic instability. HOXB7 has been reported to stimulate NHEJ-mediated DNA repair and to confer resistance to ionizing radiation (Rubin et al., 2007). This activity was associated with the ability of HOXB7 to bind Ku proteins. Ku proteins form a complex that binds to the ends of DSBs (Lieber et al., 2003). On the other hand, DLX4 has been reported to inhibit expression of BRCA1, a component of the HR-mediated DNA repair pathway (Kluk et al., 2010). Overexpression of SIX1 has been found to lead to genomic instability by attenuating the G_2-M DNA damage checkpoint (Coletta et al., 2008). In these studies, the functions of HOXB7, DLX4 and SIX1 were studied in breast cancer cells. However, these homeoproteins are also overexpressed in ovarian cancers (Naora et al., 2001b, Hara et al., 2007; Behbakht et al., 2007), and might potentially contribute to DNA repair infidelity and genomic instability in ovarian cancer cells.

4.5 Invasion and metastasis

The ability of tumor cells to invade adjacent tissues and colonize distant sites is another well-established hallmark of cancer (Hanahan & Weinberg, 2000). The lethality of ovarian

cancer stems from its propensity for aggressive intraperitoneal dissemination, with 70% of patients presenting with advanced-stage disease. FGF-2 stimulates cell migration, and advanced-stage ovarian cancers express a gene signature associated with FGF-2 signaling (De Cecco et al., 2004). HOXB7 induces FGF-2 expression in OSE-derived cells (Naora et al., 2001b) and inhibiting *HOXB7* expression in ovarian cancer cells inhibits invasiveness (Yamashita et al., 2006). Invasiveness of ovarian cancer cells is also inhibited when *HOXB13* expression is suppressed (Yamashita et al., 2006). Overexpression of *SIX1* increases metastasis of rhabdomyosarcoma by inducing expression of the cytoskeletal protein ezrin (Yu et al., 2004), but it is not known whether *SIX1* promotes ovarian cancer dissemination by the same mechanism. Conversely, *BARX2* inhibits invasiveness of ovarian cancer cells and loss of *BARX2* in ovarian cancers is associated with adverse survival (Sellar et al., 2001). The tumor-suppressive property of *BARX2* has been attributed in part to its ability to induce expression of the cell adhesion molecule cadherin-6 (Sellar et al., 2001).

Functions of several other homeobox genes that have been implicated in ovarian tumor progression are more complex. In addition to its anti-proliferative effect, TGF-β is well-known to induce epithelial-to-mesenchymal transition (EMT) and metastasis (Siegel and Massagué, 2003). We have found that DLX4 not only blocks the anti-proliferative effect of TGF-β by sequestering Smad4, but also partially inhibits TGF-β-induced EMT (Trinh et al., 2011). The ability of DLX4 to inhibit TGF-β-induced EMT could explain the reported association of DLX4 with favorable prognosis in lung cancer patients and its metastasis-suppressive activity (Tomida et al., 2007). On the other hand, we have found that DLX4 expression in ovarian cancers is strongly associated with disease progression (Hara et al., 2007). This association is likely to be due to the ability of DLX4 to stimulate other tumor-promoting processes via its induction of c-Myc, FGF-2 and vascular endothelial growth factor (VEGF) (Hara et al., 2007; Trinh et al., 2011). Another example of a homeobox gene with paradoxical functions is *HOXA4*. Whereas *HOXA4* is more highly expressed in invasive than in non-invasive ovarian cancers, *HOXA4* inhibits ovarian cancer cell migration (Klausen et al., 2009). These authors have speculated that increased *HOXA4* expression in invasive cancers might constitute a homeostatic response.

In contrast to many other types of cancers, ovarian cancer rarely spreads by hematogenous routes. Ovarian cancer cells typically disseminate by intraperitoneal 'seeding' whereby exfoliated tumor cells are transported throughout the pelvic cavity by the peritoneal fluid and frequently implant onto the mesothelial linings of the cavity wall and omentum (Naora & Montell, 2005). Attachment of ovarian cancer cells to mesothelial surfaces is mediated in part by interactions between ECM proteins and integrins (Heyman et al., 2008). We have found that HOXA10 stimulates attachment of OSE-derived cells to omental mesothelial cells by inducing expression of αvβ3 integrin (Ko et al., 2010). The *ITGB3* gene that encodes β3 integrin has also been reported to be a transcriptional target of HOXA10 in endometrial cells (Daftary et al., 2002). However, comparison of our studies of HOXA10 in ovarian and endometrial cancers reveals striking differences as well as similarities. We have found that gain of *HOXA10* expression in endometrioid ovarian carcinomas is associated with endometrial-like differentiation (Cheng et al., 2005), whereas *HOXA10* down-regulation in endometrial carcinomas correlates with loss of glandular differentiation (Yoshida et al., 2006). Consistent with these observations, *HOXA10* promoted homophilic cell adhesion in both endometrial cancer cells and OSE-derived cells (Yoshida et al., 2006; Ko et al., 2010). However, whereas *HOXA10* expression in endometrial cancer cells inhibited invasiveness

and metastasis (Yoshida et al., 2006), *HOXA10* activation in OSE-derived tumor cells lead to increased numbers of peritoneal implants by enabling tumor cells to escape anoikis and stimulating their attachment to mesothelial surfaces (Ko et al., 2010). These studies indicate that cellular behavior induced by a homeobox gene can differ depending on the cell type and context, and highlight fundamental differences between intraperitoneal seeding of ovarian cancer and 'classic' metastasis of endometrial and many other types of carcinomas.

4.6 Angiogenesis

Angiogenesis is a well-established hallmark of cancer that has been extensively studied in ovarian cancer. The angiogenic factors VEGF, FGF-2 and IL-8 are overexpressed in ovarian cancers and tumor microvessel density is a strong predictor of outcomes (Hollingsworth et al., 1995; Yoneda et al., 1998). VEGF is also the causative factor of ascites (Zhang et al., 2002). We have found that DLX4 expression in ovarian cancers is strongly associated with ascites and reduced overall survival in patients (Hara et al., 2007). Furthermore, we have demonstrated that overexpression of DLX4 in ovarian cancer cells promotes ascites and increases tumor microvessel density in mouse xenograft models. This activity of DLX4 was attributed to its induction of FGF-2 and VEGF expression (Hara et al., 2007). HOXB7 has also been found to induce FGF-2 and VEGF expression in breast cancer cells (Caré et al., 2001), and might stimulate angiogenesis in ovarian cancer by the same mechanism.

4.7 Implications for therapy

To date, functions of homeobox genes have not been described in replicative immortality or in emerging hallmarks and enabling characteristics of cancer such as deregulated cellular energetics, inflammation and evasion of immune destruction (Hanahan & Weinberg, 2011). Because homeoproteins control expression of numerous genes in different cell types and in response to different cellular signals, it is likely that misexpressed homeoproteins also modulate tumor pathogenesis by regulating one or more of these other hallmark capabilities. One central finding that has emerged from recent studies is that misexpression of an individual homeoprotein can promote multiple hallmark capabilities (Table 2).

	DLX4 ↑	DLX5 ↑	HOXB7 ↑	HOXB13 ↑	HOXA10 ↑	SIX1 ↑	PAX2 ↑	MSX2 ↑	BARX2 ↓
Sustained proliferative signaling	+	+	+			+		+	
Evasion of growth suppressors	+								
Resistance to cell death	+			+	+	+	+		+
DNA repair / Genomic instability			+			+			
Invasion / Metastasis	?		+	+		?			+
Angiogenesis	+		+						

Table 2. Implicated functions of up- (↑) and down- (↓) regulated homeobox genes in ovarian cancer.

This raises the possibility that homeoproteins could be attractive therapeutic targets. The most significant challenge to effectively inhibiting an overexpressed homeoprotein in tumors is specificity. As discussed earlier, different homeoproteins particularly within a family have highly conserved domains. One approach by which HOX protein activity can be

inhibited in cells is by using a cell-penetrating peptide that blocks interactions between HOX and PBX proteins. This peptide has been reported to inhibit growth of ovarian cancer cells (Morgan et al., 2010). However, it should be noted that many different HOX proteins are expressed in normal cells as well as in tumors and utilize PBX proteins as co-factors (Chang et al., 1995; Shanmugam et al., 1999). On the other hand, the studies to date indicate that distinct sets of homeoproteins control cell cycle progression and cell survival. Homeoproteins might therefore be useful as markers for predicting responsiveness to chemotherapeutic agents.

5. Mechanisms of homeobox gene deregulation in tumors

As discussed above, studies of *NKX3.1* and *CDX2* have demonstrated that misexpression of homeobox genes can induce pre-neoplastic lesions or predispose cells to transformation (Kim et al., 2002a; 2002b; Chawengsaksophak et al., 1997). Studying how homeobox genes are deregulated in tumors could therefore provide important insights into cancer risk. However, the mechanisms that cause aberrant expression of homeobox genes in solid tumors are poorly understood. Mutations in homeobox genes are associated with many developmental abnormalities (Mortlock and Innis, 1997; Ruf et al., 2004), but have rarely been detected in solid tumors. Deregulation of many *HOX* genes in leukemias and some *PAX* genes in sarcomas has been attributed to chromosomal translocations (Samuel & Naora, 2005; Argiropoulos & Humphries, 2007). A few homeobox genes localize to 'hot-spots' that undergo loss of heterozygosity (LOH) or are amplified in tumors. The *HOXB* gene cluster and *DLX4* map to the 17q21.3-q22 region, a 'hot-spot' that is amplified in ~10% of breast and ovarian cancers (Watanabe et al., 2001; Hyman et al., 2002; Hirasawa et al., 2003). However, overexpression of *HOXB7* and *DLX4* occurs in >50% of breast and ovarian cancers (Naora et al., 2001b; Man et al., 2005; Wu et al., 2006; Hara et al., 2007), indicating that gene amplification is not the sole mechanism underlying the overexpression of these genes. On the other hand, *NKX3.1* maps to 8p21, a region that is deleted in ~80% of prostate cancers (He et al., 1997). *BARX2* is located at 11q24-q25, within a minimal region that is associated with frequent LOH and adverse survival in ovarian cancer (Gabra et al., 1996). It is interesting to note that *BARX2* is the only homeobox gene with tumor-suppressive properties that has been identified to be lost in ovarian cancer. In contrast, other homeobox genes have been found to be overexpressed in ovarian cancers (Table 2). In this regard, the pattern of misexpression of homeobox genes in ovarian cancers is remarkably more similar to that in hematologic malignancies rather than in other solid tumors.

5.1 Developmental signals

Little is known about the signaling pathways that control expression of homeobox genes in tumors. However, studies from the developmental biology field can provide important insights. Cross-regulatory interactions have been reported between bone morphogenetic proteins (BMPs) and *DLX* genes during normal cell differentiation. For example, BMP-2 activates *Dlx3* transcription (Park & Morasso, 2002), whereas Smad6, an antagonist of BMP signaling, inhibits DLX3 transcriptional activity (Berghorn et al., 2006). We have observed that levels of DLX4 protein decrease in cells following TGF-β stimulation (Trinh et al., 2011). This raises the possibility that DLX4 is a component of a regulatory loop that blocks TGF-β signaling and is conversely regulated by TGF-β. There is considerable evidence that

patterning of the reproductive tract is controlled by a regulatory network of distinct sets of Wnts and homeobox genes (Kobayashi & Behringer, 2003). *MSX2* is a transcriptional target of β-catenin/TCF and *MSX2* expression is increased in endometrioid ovarian carcinomas with deregulated β-catenin (Zhai et al., 2011). Expression of *AbdB HOX* genes in the endometrium is also tightly regulated by estrogen and progesterone (Ma et al., 1998). WT1 is a transcription factor that is used as a marker of serous ovarian cancer and reportedly represses *HOXA10* expression (Andikyan & Taylor, 2009). WT1-mediated repression could explain why many serous ovarian cancers do not express *HOXA10* (Cheng et al., 2005).

5.2 Epigenetic mechanisms

DNA methylation is the most commonly identified mechanism that silences expression of homeobox genes in solid tumors such as breast and lung cancers (Novak et al., 2006; Rauch et al., 2007). We have found that *HOXA10* down-regulation in high-grade endometrial carcinomas is due to promoter methylation (Yoshida et al., 2006). DNA methyltransferases that methylate DNA are recruited by Polycomb repressive complexes (Mills, 2010). Polycomb and Trithorax group proteins form multi-protein complexes that contain histone methyltransferase activity and dynamically alter chromatin structure by modifying specific residues in histone tails. Polycomb group proteins keep *HOX* genes repressed, whereas Trithorax group proteins counteract Polycomb-mediated silencing and maintain *HOX* expression (Soshnikova & Duboule, 2009). Polycomb and Trithorax group proteins are aberrantly expressed in different types of cancers (Mills, 2010), but it is unclear whether altered expression of these proteins causes *HOX* activation in ovarian cancers. A striking aspect of *HOX* gene clusters is the presence of long noncoding RNAs and microRNAs in the intergenic regions. These non-coding RNAs control transcription of *HOX* genes through a variety of *cis*- and *trans*- acting mechanisms (Lemons & McGinnis, 2006; Yekta et al., 2008). One intriguing example is the long non-coding RNA *HOTAIR*. *HOTAIR* is located in the *HOXC* locus and interacts with and targets the Polycomb repressive complex 2 (PRC2) to the *HOXD* locus located on a different chromosome (Rinn et al., 2007). *HOTAIR* expression in primary breast tumors has been found to be a strong predictor of metastasis (Gupta et al., 2010). Enforced expression of *HOTAIR* in cancer cells increased metastasis by inducing genome-wide re-targeting of PRC2 to an occupancy pattern that resemble that of embryonic fibroblasts (Gupta et al., 2010). Almost all homeobox genes that have been studied in ovarian cancer are overexpressed (Tables I,II), and their activation in tumors might arise from down-regulation of non-coding RNAs. Indeed, microRNA-185 has been reported to target *Six1* and is expressed at decreased levels in ovarian cancers (Imam et al., 2010).

6. Conclusions

In conclusion, the functional significance of homeobox genes in ovarian cancer is rapidly emerging as an intriguing research area that provides new molecular insights into the histogenesis of the different subtypes of ovarian cancer and the progression of this disease. The studies to date raise the possibility that specific sets of homeoproteins might serve as diagnostic or predictive markers in the appropriate settings and in combination with other markers. However, more mechanistic studies are essential to further develop our understanding of the functions of homeobox genes in ovarian cancer biology and to translate this research into clinical applications. In particular, the target genes of

homeoproteins and the mechanisms that cause aberrant homeobox gene expression in tumors need to be identified. It is also important to determine whether a given homeobox gene controls a cellular process by the same mechanism in cells of different lineages, or has cell type-specific effects. Studies from the developmental biology field have provided powerful insights into the regulation, functions and mechanisms of homeobox genes in human cancers. Stronger integration between the developmental and cancer biology fields will be instrumental for furthering our understanding of the functional significance of homeobox genes in ovarian cancer.

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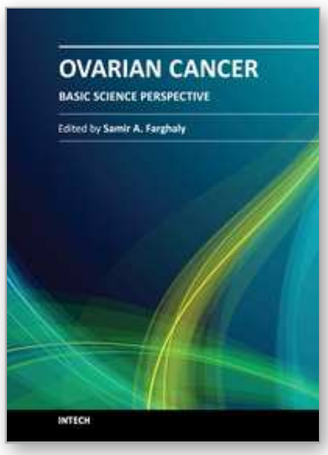
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Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details the molecular biological aspects of ovarian cancer. It provides molecular biology techniques of understanding this cancer. The techniques are designed to determine tumor genetics, expression, and protein function, and to elucidate the genetic mechanisms by which gene and immunotherapies may be perfected. It provides an analysis of current research into aspects of malignant transformation, growth control, and metastasis. A comprehensive spectrum of topics is covered providing up to date information on scientific discoveries and management considerations.

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