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Derleme

Homeobox (HOX) Genes and Gynecological Cancers

Homeobox (HOX) Genleri ve Jinekolojik Kanserler

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ÖZET

Özet: Homeobox (HOX) genleri bir transkripsiyon faktörü olarak, embriyonik gelişim ve kanser ilerlemesinde önemli bir rol oynar. Ayrıca dişi üreme yolunun uygun şekilde bölünmesini sağlar ve yetişkin kimliğine yol açan konumsal kimliği verir. HOX genlerinin jinekolojik kanserlerde farklı ekspresyon paterni sergilediği, diyagnostic belirteç olmanın yanı sıra prognostik belirteç olarak kullanılabileceği öngörülmektedir. HOX genlerinin jinekolojik kanserlerin onkogenezindeki rolüne ilişkin bilgilerimiz gelişmektedir. Burada HOX genlerinin insan gelişimi ve jinekolojik kanser onkogenezindeki rollerini gözden geçiriyoruz.

Anahtar Kelimeler: Homebox genleri, Jinekolojik Kanserler, Onkogenez, Embriyogenezis

ABSTRACT

Summary: Homeobox (HOX) genes play a significant role as a transcription factor in embryonic development and cancer progression. In addition, it ensures appropriate division of the female reproductive tract and determines spatial identity that leads to adult identity. It has been predicted that HOX genes exhibit a different expression pattern in gynecological cancers and can be used as a prognostic marker as well as a diagnostic marker. Our scientific knowledge has broadened regarding the role of HOX genes in the oncogenesis of gynecological cancers. Here, we review the role of HOX genes in human development and oncogenesis of gynecological cancers.

Key words: Homebox genes, Gynecological Cancers, Oncogenesis, Embryogenesis

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Introduction

The Homeobox (HOX) genes are a family of transcription factors that function as primary regulators of development in mammalians and play a role in several biological pathways, including hemostasis, cell differentiation and organ functioning. The HOX genes were first described by their roles in driving extremity and organ development at the anterior-posterior axis and cell differentiation processes in fruit fly "Drosophila melanogaster". Structural anomalies resulting from alterations in HOX gene expression indicate that they play a significant role in embryogenesis (1,2). In addition to their critical roles in the development of the embryos, studies showed that the dysregulation of HOX gene expression played a role in human carcinogenesis. In many studies, it was observed that the expression of HOX genes increased in cancer cells and HOX genes affected several signal pathways as a transcriptional factor.

In this review, we aimed to discuss the role of HOX genes in human development and gynecological cancer development.

Role of HOX genes in human development

In humans, there are 39 HOX genes arranged in four paralogous clusters (A, B, C, D) localized at chromosomes 7p15, 17q21, 12q13 and 2q31. Each cluster includes 9-11 paralogous HOX genes numbered between 1 and 13 according to HOX sequence similarity and 3' to 5' chromosomal location (3). (Table 1).

The arrangement of these genes and chromosomes shows temporal and spatial collinearity; the HOX genes at 3' terminal are expressed at earlier development period and in anterior body regions while those at 5' terminal at later development and in posterior body regions. For instance, 5' genes (paralogous 9-13) play a role in genitourinary structures in the lumbosacral region. During development, they aid apoptosis and modeling of tissues and organs (3,4). The HOX gene mutations in Drosophila may lead to changes in segmental identity, particularly in the development of anterior regions; however, these variants are not as severe in mammalians. This may be due to the overlapping of genetic functions among HOX gene clusters (1,2). Many developmental defects resulting from mutations in HOX genes have been defined in humans. For instance, human synpolydactyly is an autosomal dominant limb deformity caused by a mutation in the HOXD13 gene. Supplementary digit development is observed in hands and feet in individuals with heterozygous HOXD13 gene mutation, while more severe forms of hand-foot bone malformations is present in individuals with homozygous mutations. Again, the hand-foot-genital (HFG) syndrome is an autosomal syndrome resulting from the HOXA13 mutation. This anomaly affects the development of the thumb and toe as well as the urethra and Müllerian duct (2).

Reproductive tract development and HOX genes

The HOX genes regulate the development axis in the embryonic period; in addition, in the female reproductive tract, the Müllerian duct provides segmental identity by expression of HOXA genes at certain regions. Specifically, HOXA9 regulates differentiation of fallopian tubes, while HOXA10, HOXA 11 and HOXA 13 regulate differentiation of developing uterus, lower uterine segment and cervix and upper vaginal segment,

Table 1. Hox genes in human

HOXA	Chromosome 7p15	HOXA1, HOXA2, HOXA3, HOXA4, HOXA5, HOXA6, HOXA7, HOXA9, HOXA10, HOXA11, HOXA13
HOXB	Chromosome 17q21	HOXB1, HOXB2, HOXB3, HOXB4, HOXB5, HOXB6, HOXB7, HOXB8, HOXB9, HOXB13
HOXC	Chromosome 12q13	HOXC4, HOXC5, HOXC6, HOXC8 ,HOXC9, HOXC10, HOXC11, HOXC12, HOXC13
HOXD	Chromosome 2q31	HOXD3, HOXD4, HOXD8, HOXD9 ,HOXD10 ,HOXD11, HOX12, HOXD13

respectively (5,6,7). HOX genes create a special identity for the endometrium, which alters during the menstrual cycle in adults. The cyclic proliferation of endometrium depends on regular estrogen and progesterone production. The HOX gene expression is regulated by sex steroids, which plays a significant role in endometrial development and receptivity.

Specifically, Hoxa10/HOXA10 and Hoxa11/HOXA11 are expressed in the endometrium of adult rats and humans. The expression of two genes alters depending on the menstrual cycle. The Hoxa10/HOXA10 and Hoxa11/HOXA11 are expressed in the proliferative phase and the expression is enhanced during the secretory phase. Also, these HOX genes are essential for embryo implantation. In adults, permanent HOX gene expression may be a mechanism to protect developmental plasticity in the female reproductive tract (5,8,9).

It has been reported that HOXA7 is effective in ovarian folliculogenesis but not in primordial follicles and its expression is higher in primary and mature follicles.

During follicular maturation, the sub-cellular localization of HOXA7 becomes cytoplasmic with nuclear dominancy. This differing localization demonstrates that HOXA7 undergoes cell type- and phase-specific modifications during human ovarian folliculogenesis (10,11).

Role of HOX genes in cancer

There is a close association among developmental arrangement, embryogenesis and carcinogenesis. In adult tissues, HOX genes play a role in several biological pathways, including homeostasis, cell differentiation and maintaining organ functions (11). In adult tissues, HOX gene expression generally represents embryonic expression; however, in different cancers, it shows alterations from normal expression in adults. In a tumor of certain tissue, HOX gene expression may differ from expression seen in normal tissues in a temporospatial manner and/or there may be an increased HOX gene expression than normal expression pattern (2).

The HOX genes may act as transcription activators or suppressors and have well-known roles as oncogene or tumor suppressor in different cancers (12,13). The HOX genes leading to metastasis and treatment resistance by triggering cell proliferation at the cellular level, preventing apoptosis and promoting angiogenesis in the tumoral level indicate that HOX genes play a proto-oncogenic role. In addition, epigenetic changes may cause down-regulation or inhibition of certain HOX genes normally functioning as tumor suppressors (4,15,16).

The association between HOX genes and cancer was detected in hematological malignancies for the first time; however, recently, it has been found that they play a role in many solid tumors, including breast cancer, colon cancer, prostate cancer, lung cancer and gynecological cancer (15).

HOX genes and gynecological cancers

Hox genes and epithelial ovarian cancer

Epithelial over cancer (EOC) is the leading cause of death related to gynecological cancers, with a 5-years survival rate of 30-40% in advanced disease. The EOC accounts for 90% of all ovarian cancers and has histological subtypes, including serous carcinoma, endometrioid carcinoma, mucinous carcinoma and clear cell carcinoma.

In recent studies, the findings showed that EOC subtypes were different clinic-pathological disorders having distinct abnormal HOX gene expression patterns which affected prognosis and treatment response. It was observed that specific HOX gene expression assigned a certain identity and phenotype to cancer cells (6,12).

A range of somatic copies was reported in three members of the HOXB family, namely HOXB2, HOXB5 and HOXB8, in the genomic analysis of high-grade ovarian cancer in The Cancer Genome Atlas (TCGA). On the basis of gene expression, the high-grade ovarian cancers were divided into four distinct expression subtypes: immunoreactive, differentiated, proliferative and mesenchymal and the high expression level of HOX genes (HOXB2, B5 and B8) was identified as a characteristic of mesenchymal subtype (17).

In several studies, low and high expression levels of different HOX genes were observed. In a study conducted by Kelly et al., HOX A13, B6, C13, D1 and D13 were associated with a poor prognosis in high-grade serous ovarian carcinoma (18). In another study, the findings showed that 11 HOX genes (A7, B3, B4, B6, C10, C11, D1, D3, D10, D11, D13) were either up-regulated or down-regulated in serous ovarian carcinoma and that HOXB3 expression was significantly higher at RNA and protein level in malignant cases (13).

In a study, it was reported that HOXA5, B2, B5, B6, B7 and D1 were up-regulated and that HOXC6 was down-regulated in malignant ovarian tissue (19, 20). In several studies, the heterogeneous results were shown due to heterogeneous genomic structure in ova-

rian cancer, particularly in high-grade serous ovarian carcinoma (21). Cheng et al. reported that HOX genes regulated Mullerian duct differentiation and that they were expressed in epithelial ovarian cancers but not in the normal ovarian surface epithelium. It was observed that overexpression of HOXA9, HOXA10 and HOXA11 determined the histological identity of serous papillary, endometrioid and mucinous EOCs, respectively (6, 22). (Table 2). Again, it was observed that HOXA7 was abnormally expressed in ovarian cancer tissues with Müllerian-like features; however, it was barely or not expressed in undifferentiated ovarian cancers and normal ovarian surface epithelium (10,11). HOXA9, HOXA10 and HOXA11 induced Müllerian differentiation ability when HOXA7 was expressed in an ectopic manner in undifferentiated ovarian tumor of rats (6).

In addition to phenotypic identification, it also played a role in the oncogenesis of ovarian cancer. HOXB7 induced mitogenic and angiogenic effects by increasing fibroblast growth factors. It was observed that the HOXB13 gene led to proliferation of ovarian cancer cell lineage in rats in vivo and in vitro through Ras activation (22, 23).

In addition to the increase in tumor proliferation, the HOXB7 and HOXB13 contributed to cancer spread by adding invasive features of ovarian cancer cells (18,19,22). HOXB7 played a role in repairing DNA double-strand breaks by interacting with DNA-dependent protein kinase holoenzyme Ku70, Ku80 and DNA-PKcs. The endogenous and exogenous HOXB7 binding to the holoenzymes enhanced DNA repair via poly (ADP) ribose polymerase (PARP) activity (19,24). In cases with high-grade serous ovarian cancer, a serum anti-HOXB7 antibody assay against HOXB7 may be used as a diagnostic tool. In clear cell ovarian carcinoma, HOXA10 can be used as a prognostic marker and its overexpression is associated with poor prognosis (19).(Table 3).

In ovarian carcinoma, a high level of HOX gene expression makes them a potential therapeutic target. The use of a peptide, HXR9, which disrupts the interaction between HOX proteins and cofactor PBX, prevents binding of HOX/PBX dimer to its target, hampers target gene transcription and induces apoptosis by acting as a specific competitive inhibitor of HOX/PBX interaction (14,22,25).

The HOX gene expression was different in platinum-resistant and platinum-sensitive serous ovarian cancers. HOXB4 and HOXB9 overexpression was observed in platinum-resistant cell lines. Targeting HOX/PBX dimer presents a novel therapeutic option in platinum-resistant cancers, which should be supported by further studies (19).

In conclusion, HOX genes drive tumor formation and progression by regulation processes, such as tissue identity regulation, differentiation, proliferation, adhesion, migration and apoptosis in EOC. The variable expression and function of HOX genes may play a critical role in the diagnosis and prognosis of EOC and can serve as a predictive biomarker for response to chemotherapy.

Hox genes and endometrial cancer

Endometrial cancer is the most common gynecological cancer and the fourth most common cancer among women. The role of HOX gene is well-defined in the differentiation of embryonic tissues. HOXA10 gene is expres-

Table 2. Hox gene expression in histologic subtypes of ovarian cancer

HOX genes	Normally expressed tissue	EOC cancer expression
A7, A9	Fallopian Tubes	Serous, mucinous, endometrioid
A10	Endometrium	Mucinous, endometrioid
A11	Endoservix	Mucinous

Table 3. The role of Hox genes in EOC

Proliferation	HOXB7, HOXB13, HOXA10
Motility and spread	HOXB7, HOXB13, HOXB4
DNA repair	HOXB7
Phenotype	HOXA7, HOXA9, HOXA10, HOXA11

sed in the developing uterus. In addition, the HOXA10 gene is expressed in the endometrium of adults and its expression varies throughout the menstrual cycle. It was shown that HOXA10 expression drastically increased during embryo implantation in the mid-luteal phase and remained high during the luteal phase (5). As it was observed that the HOX gene expression differed by differentiation of endometrium, alterations in HOX gene expression were investigated in endometrial hyperplasia and adenocarcinoma in several studies. A marked increase was detected in HOXA10 expression in high-grade endometrial adenocarcinoma. The increased nuclear grade is associated with poor prognosis in endometrial cancer. Thus, HOXA10 may be used to distinguish aggressive endometrial cancer from less aggressive malignancies (26). The HOXA10 expression may also be used as a marker for high nuclear grade independently from ER, PR and p53 (26).

HOXD10 is another gene evaluated in endometrial adenocarcinoma. The HOXD10 expression decreased in endometrial adenocarcinoma when compared to normal endometrium. In addition, HOXD10 expression was significantly decreased by advancing grade (27). Wang et al. demonstrated that HOXB9 expression increased and was associated with histological grade and lymph node metastasis in endometrial cancer and that high levels of HOXB9 were associated with poor prognosis in patients with endometrial cancer. The authors also suggest that HOXB9 can be a novel prognostic marker in endometrial cancer (28).

Hox genes and cervical cancer

Although the primary etiological agent is the human papillomavirus in cervix cancer, it is a multifactorial disease associated with genetic, environmental and epigenetic factors. In addition, the alteration in transcription factors is a crucial factor in the development of cervix cancer. HOX genes have a significant role as developmental genes during embryogenesis and that abnormal HOX gene expression has a critical role in developing several tumors.

The role of HOX genes in the development of neoplastic cervical cells was elucidated by the finding that up-regulated HOXA1, HOXA5 and HOXA6 expressions were associated with poor overall survival and increased mortality (29). A study focusing on HPV 16 E7-mediated epigenetic regulation of HOX genes showed that HPV16 E7 had the main regulatory role in the modulating HOX gene expression. These results showed that abnormal expression of HOX-related genes was associated with cervical carcinogenesis. A strong correlation was found between squamous cell cervical cancer and high HOX gene expression (30).

In cytological and surgical specimens, the HOX gene expression analysis may be helpful to identify the cervix cancer with poor prognosis and more aggressive treatments or closer follow-up may be recommended to high-risk patients. Novel agents may be used to treat refractory cervical cancer by developing agents that inhibit HOXA gene expression.

Conclusion

The HOX genes are a family of transcription factors which is primary regulators of development. In addition to their role in embryogenesis, they also have critical roles in cell survival and proliferation, cell motility, differentiation of tissue-specific lineage and coordinating the immune response to tumor cells in oncogenesis. In gynecological cancers, they can be used as both diagnostic and prognostic biomarkers. In addition, it can be used as a predictive marker for platinum sensitivity in epithelial ovarian cancer. Targeting HOX genes is offered as a novel therapeutic modality in platinum-resistant cancers, but further studies should be conducted.

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