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Mini Review

## ***HOX* Genes as Potential Markers of Circulating Tumour Cells**

Richard Morgan and Mohamed El-Tanani

Institute of Cancer Therapeutics, Faculty of Life Sciences, University of Bradford, UK

Running title: *HOX* Genes and CTCs

**Keywords:** Circulating tumour cells; *HOX* gene; biomarker

### **Abbreviations**

CTC, circulating tumour cell

EpCam, epithelial cell adhesion molecule

## **Abstract**

Circulating tumour cells (CTCs) have significant diagnostic potential as they can reflect both the presence and recurrence of a wide range of cancers. However, this potential continues to be limited by the lack of robust and accessible isolation technologies. An alternative to isolation might be their direct detection amongst other peripheral blood cells, although this would require markers that allow them to be distinguished from an exceptionally high background signal. This review assesses the potential role of *HOX* genes, a family of homeodomain containing transcription factors with key roles in both embryonic development and oncogenesis, as unique and possibly disease specific markers of CTCs.

## Introduction

Circulating tumour cells (CTCs) have been identified for a wide range of cancers types, although notable examples include breast [1], prostate [2], colorectal [3], and lung cancer [4]. In addition to providing a mechanistic explanation for widespread disease dissemination, they also represent a potential biomarker for diagnosis and prognosis. Hence, for example in breast cancer the presence of CTCs is an independent prognostic factor for both progression-free survival and overall survival, and a cut-off of 5 CTCs / 7.5 ml has been used to identify patients with a good or poor prognosis [5]. In addition, the persistence of CTCs after adjuvant therapy for breast cancer is significantly associated with a shorter disease-free survival.

Although CTCs are a potentially useful biomarker, an intrinsic difficulty of this approach is their rarity, and their identification requires a combination of enrichment and detection strategies. The latter is based on technologies that can distinguish CTCs from blood cells based on their physical (e.g. size, density, electrical charge and deformability), and biological properties (e.g. cell surface protein expression and viability). Ficol gradients are one of the simplest and earliest methods used to separate CTCs, but other available methods include the use of dielectrophoretic technology to exploit differences in the biophysical properties of CTCs and blood cells [6], and label-free chips that separate CTCs based on their size [7]. Most techniques used to enrich CTCs are based on the expression of distinct cell surface markers that can be immunologically detected. The most commonly exploited cell surface marker is the epithelial cell adhesion molecule (EpCam), which is central to a range of antigen-capture based techniques such as CellSearch<sup>®</sup> and CTC-CHIP [8, 9]. However, there are no uniformly expressed CTC markers, and EpCam itself is not present on all CTCs, most notable because it is down regulated during the epithelial-to-mesenchymal transition, a process that is central to metastatic change [10].

An alternative to CTC isolation could be the identification of gene expression patterns that are not present in blood cells. This would inevitably be complicated by the vast excess of RNA from white blood cells in any preparation made from whole blood. However, sensitive detection methods for identifying a small number of transcripts, for example quantitative PCR (qPCR), could allow CTCs to be identified, as well as potentially the cancer from which they originated, if specific patterns of gene expression could be established that are not presented by white blood cells. One particularly strong candidate in this respect is the *HOX* gene family.

### ***HOX* genes**

The *HOX* genes are a family of homeobox-containing transcription factors that have a crucial role in the patterning of the early embryo, as well as some more limited functions in adult physiology. There are 39 *HOX* genes in the human genome present in 4 separate genomic clusters, named A-D, which arose from a series of duplication events prior to the emergence of mammals [11]. Unusually, genes within each cluster share enhancer regions, leading to a closely coordinated pattern of expression during development and a close relationship between the position of each *HOX* gene in the cluster and its temporal and spatial expression. Thus, for example, the 3' most member of the *HOXB* cluster, *HOXB1*, is expressed earlier and more anteriorly than one of the most 5' members, *HOXB9* [12]. *HOX* proteins have relatively limited specificity for DNA, binding to a 4 base pair sequence. Their binding specificity and hence target gene activation (or in some cases repression) is greatly enhanced by their interaction with specific co-factors such as *PBX* and *MEIS* proteins [13, 14].

During early development, *HOX* gene products help to define the identity of the tissues in which they are expressed, principally along the anterior to posterior axis. These tissues include the nervous system posterior to the midbrain, the gut, and the limbs [11]. In addition, some adult cells continue

to express *HOX* genes and in these cells *HOX* expression is necessary to maintain cellular identity, and in some cases is also needed for continued cell proliferation and survival. One of the best characterized examples is the hematopoietic stem cell and its differentiated progeny. *HOXB4* is required for the continued proliferation of hematopoietic stem cells, and once their daughter cells subsequently begin to differentiate through the long cascade of hematopoietic progenitor cell types they express different *HOX* genes in nested patterns, with the mature lymphocytes expressing quite distinct patterns of *HOX* genes compared to the parental stem cells [15].

### ***HOX* genes in cancer**

In addition to their function in the embryo and in some normal adult cells, the *HOX* genes also have a key function in malignancy. This has been reviewed extensively elsewhere, but in brief, the *HOX* genes are frequently dysregulated in almost all of the solid and haematological malignancies in which they have been studied [16]. A number of them have been shown to function as oncogenes, including *HOXA9*, the forced expression of which in normal mouse bone marrow cells leads to acute myeloid leukaemia within 3 months [17]. Many other *HOX* genes have been shown to have a pro-oncogenic role in terms of supporting tumour growth. *HOX* proteins can promote cell proliferation and survival through interaction with the PBX co-factor, and the disruption of *HOX*/PBX dimer formation using the HXR9 peptide has been shown to trigger apoptosis in a wide range of solid malignancies both *in vitro* and *in vivo* [18-23]. Furthermore, *HOX* expression has been shown to promote a number of aggressive tumour characteristics, including invasion and migration [24], DNA repair [25], and the induction of angiogenesis [26]. Consequently, the tumour expression of a number of *HOX* genes has been shown to be related to the survival of cancer patients [27].

Despite a number of excellent reviews on this subject, the *HOX* expression profiles of different cancer types generally remains unclear as it is difficult to directly compare the information in studies that have used different techniques to assess *HOX* expression, and some studies have given conflicting results. This review attempts to establish a broad overview of *HOX* expression in different solid malignancies by only including data on the over- or under-expression of *HOX* genes based on at least 2 different techniques (e.g. QPCR and immunohistochemistry), and which has been demonstrated in 2 different studies. The findings of this review for head and neck [24, 28-36], oesophageal [37, 38], gastric [39, 40], colorectal [41], pancreatic [42], hepatic [41], lung [43-46], breast [47], bladder [48, 49], renal [23], prostate [50, 51], and ovarian cancer [52-54] are summarized in Fig 1 and Table 1. It is striking that different tumour types show very different patterns of *HOX* expression. For example, gastric tumours tend to show very little *HOX* gene over-expression, whilst hepatic tumours exhibit a vastly dysregulated network of *HOX* genes. It also seems clear that different tumour types have radically different *HOX* gene expression patterns, with the notable exception of bladder and prostate tumours (Fig 1). These distinct, tumour-specific expression profiles make *HOX* genes potential markers of CTCs.

### ***HOX* genes as CTC markers**

As discussed above, CTCs generally make up only a very small proportion blood cells. After excluding red blood cells, the majority of remaining cells are lymphocytes and monocytes. Both have previously been shown to express *HOX* genes, and indeed the expression of all 39 *HOX* genes has been studied in different lymphocyte and monocyte populations [55]. This revealed that monocytes, T-lymphocytes and B-lymphocytes expressed distinct but also overlapping sets of *HOX* genes, and also that *HOX* gene expression changed considerably upon activation of the cell types. In contrast, very little is known of *HOX* expression in other myeloid lineages, although previous studies have

suggested that *HOX* genes are generally down-regulated in mature blood cells [56]. In the context of possible CTC markers, these data are potentially very useful as they also reveal that a number of *HOX* genes are not expressed in normal lymphocytes or monocytes (Table 2). Despite the reduced number of *HOX* genes available for possible CTC identification, all tumour types appear to present with a distinct pattern of non-lymphocytic/monocytic *HOX* expression, except for bladder and prostate tumours (Fig 2). Based on these findings, it seems possible that *HOX* expression profiles could act as a “fingerprint” of specific tumour types, potentially allowing CTC detection without CTC isolation. For example, hepatic CTCs might be distinguished by their very high level of *HOX* dysregulation, whilst gastric CTCs appear to be characterized by high levels of *HOXA13* expression in the absence of other *HOX* genes. Ovarian and pancreatic cancer is likewise distinguishable by the predominant expression of genes from the *HOXB* cluster, although the former expresses more posterior (5') *HOX* genes than the latter. It should be noted that the data presented in this review are inevitably incomplete with respect to the expression of *HOX* genes in both cancer and normal blood cells. However, it is becoming apparent that there is high degree of differential *HOX* expression between mature blood cells and CTCs, pointing towards a nucleic acid based methodology for distinguishing between these cell types.



**Table 1:** *HOX* gene expression in cancer – stages and comparators

<b><i>HOX</i> genes</b>	<b>Cancer</b>	<b>Disease stage</b>	<b>Comparator</b>	<b>Reference</b>
<i>HOXB9</i>	Head and neck		Immortalized normal oral keratinocytes, normal oral mucosa	[24]
<i>HOXA1</i>	Head and neck		Normal oral mucosa	[28]
<i>HOXB7</i>	Head and neck	I, II, III, IV	Normal oral mucosa	[29]
<i>HOXD10</i>	Head and neck	Primary, metastatic	Immortalized normal oral keratinocytes, normal oral mucosa	[30]
<i>HOXB5</i>	Head and neck	N0, N+	Normal oral mucosa	[31]
<i>HOXA10</i>	Head and neck	I, II, III, IV	Normal oral tissue	[32]
<i>HOXD10</i>	Head and neck		Immortalized normal oral keratinocytes, normal oral mucosa	[33]
<i>HOXC5</i>	Head and neck		Rat normal oral tissue	[34]
<i>HOXC6</i>	Head and neck		Normal tissue	[35]

	neck			
<i>HOXA10, A13, B7, C4, C8, D9, D10, D13</i>	Oesophageal cancer	Ila, I Ib, III	Normal oral mucosa	[37]
<i>HOXD9</i>	Oesophageal cancer		None	[38]
<i>HOXA13</i>	Gastric cancer	All T stages, metastasis	Normal mucosa	[39]
<i>HOXC6</i>	Gastric cancer		Normal mucosa	[40]
<i>HOXA9, B3, B8, B9</i>	Colorectal cancer	pT1, pT2, pT3, pT4	Normal colorectal mucosa	[41]
<i>HOXA3, A5, A6, A7, A9, A10, A11, A13, B1, B6, B7, B8, B9, B13, C5, C6, C8, C9, C10, C11, C12, C13, D1, D3, D4, D8, D9, D10</i>	Hepatic cancer	pI, pII, pIII, pIVa	Normal liver tissue adjacent to the tumour	[41]
<i>HOXB2, B5, B6, B7</i>	Pancreatic cancer	Pre-malignant pancreatic intraepithelial neoplasia, adenocarcinoma	Normal tissue	[42]
<i>HOXA1, A5, A10, C6</i>	Non-small cell lung cancer	pTNM: pT2(N0/1/2)M0 pStage: IB/IIB/IIIA	Normal tissue	[43]
<i>HOXB9</i>	Lung cancer	All clinical stages and TNM categories	Normal tissue	[46]

		assessed		
<i>HOXA1</i>	Small cell lung cancer	Extensive and limited disease	Normal lung alveoli epithelium	[45]
<i>HOXA6, A13, B2, B4, B5, B6, B7, B8, B9, C5, C9, C13, D1, D8</i>	Breast cancer		Non-malignant tissue	[47]
<i>HOXB13</i>	Bladder cancer	Muscle invasion	Non-invasive disease	[49]
<i>HOXC4, C5, C6, C11</i>	Bladder cancer		Normal uroepithelium	[48]
<i>HOXB13</i>	Prostate cancer		Normal prostate tissue	[50]
<i>HOXC4, C5, C6, C8</i>	Prostate cancer	Primary tumours, metastatic disease	Normal prostate epithelium, benign hypertrophy	[51]
<i>HOXA10</i>	Ovarian cancer		Normal ovarian tissue	[52]
<i>HOXB7, B13</i>	Ovarian cancer		Normal ovarian tissue	[53]
<i>HOXB8</i>	Ovarian cancer	Histological stages: high, low FIGO stages: IIIc, IV	Normal ovarian tissue	[54]
<i>HOXA5, A9, B5, C9, D8, D9, D10</i>	Renal cancer		Normal adjacent tissue	[23]

**Table 2:** *HOX* genes not expressed in normal lymphocytes or monocytes

<b>HOXA</b>	<b>HOXB</b>	<b>HOXC</b>	<b>HOXD</b>
<i>HOXA1</i>	<i>HOXB1</i>	<i>HOXC5</i>	<i>HOXD4</i>
<i>HOXA7</i>	<i>HOXB2</i>	<i>HOXC9</i>	<i>HOXD13</i>
<i>HOXA9</i>	<i>HOXB3</i>	<i>HOXC10</i>	
<i>HOXA11</i>	<i>HOXB5</i>	<i>HOXC11</i>	
<i>HOXA13</i>	<i>HOXB6</i>		
	<i>HOXB7</i>		
	<i>HOXB8</i>		
	<i>HOXB9</i>		
	<i>HOXB13</i>		

**Figure 1:** Summary of *HOX* gene expression in different solid malignancies.

**Figure 2:** Summary of *HOX* genes expressed in different solid malignancies that are not expressed in normal lymphocytes or monocytes.

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Figure 1

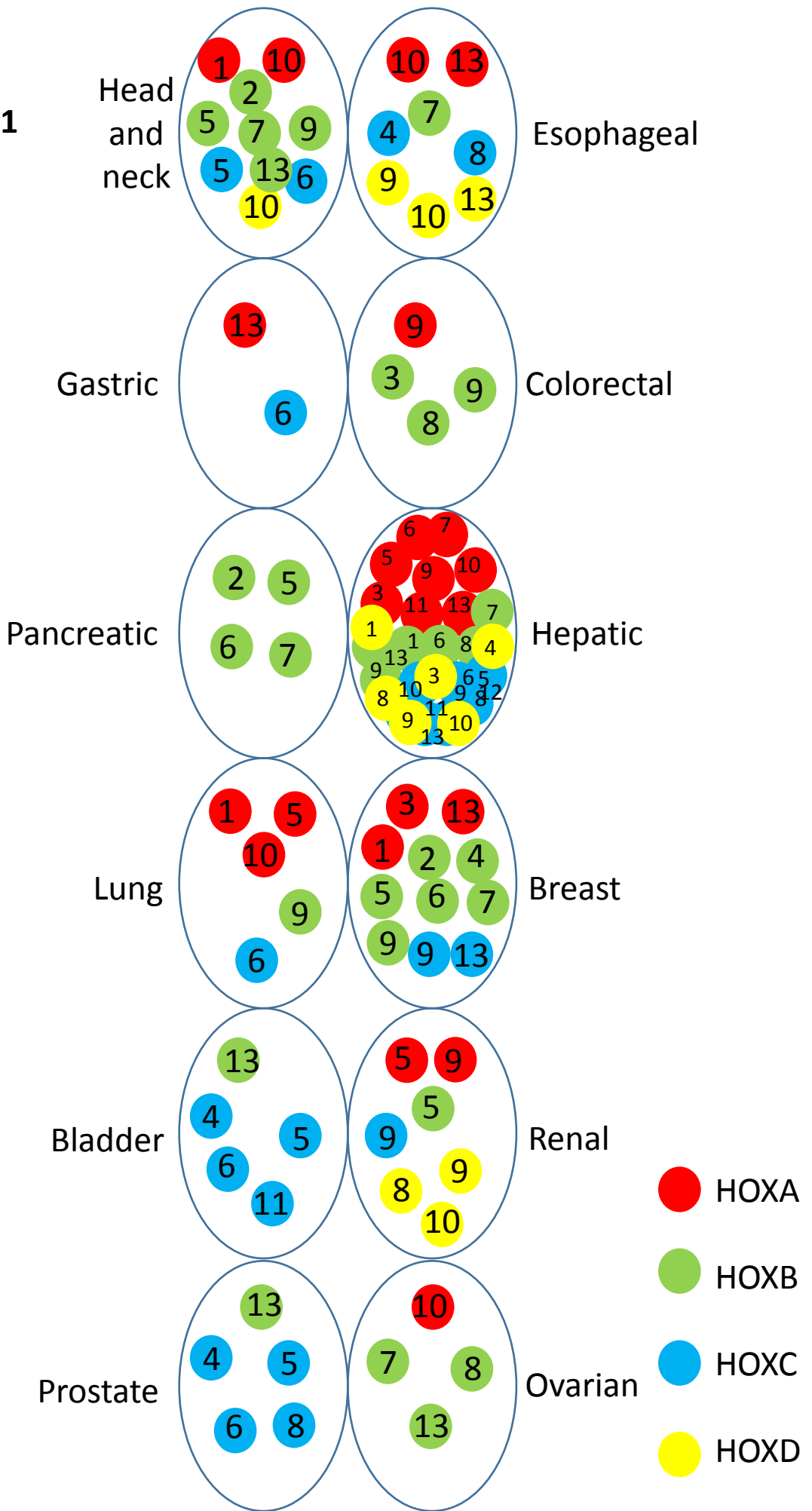




Figure 2

