The role of *HOX* genes in head and neck squamous cell carcinoma

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Abstract

Recent decades have witnessed the publication of numerous studies reporting alterations in the genome and transcriptome of head and neck squamous cell carcinoma (HNSCC). Currently, the utilisation of these alterations as biomarkers and targets for therapy are limited and new, useful molecular characteristics are being sought. Many of the published HNSCC gene expression profiles demonstrate alterations in the expression of *HOX* genes. These are a family of Homeobox containing genes which are involved in developmental patterning and morphogenesis in the embryo, and which are often aberrantly expressed in cancer. The 39 *HOX* genes found in the human genome are arranged in 4 paralogous groups at different chromosomal loci. These control a wide range of cellular processes, including proliferation and migration, which are relevant in the context of cancer development. In this review article we will outline the biology of *HOX* genes in relation to cancer and summarise the accumulating evidence for their role in the development of HNSCC and the possibility that they could be a therapeutic target in this malignancy. We will also identify areas where our current understanding is weak in order to focus future work and appraise the ongoing strategies for pharmacological intervention.

In 1894, William Bateson described structural variations and body part replacement/transformations in insects, and named this phenomenon "homeosis" (1). The discovery of gene mutations linked to homeosis continued and two homeotic gene complexes (HOM-C), which control Drosophila segmentation, were described (2, 3). Homeotic proteins encoded by the HOM-C genes were identified as transcription factors (4, 5), and for the majority of these their function is mediated by a highly conserved 180 base pair DNA sequence, the homeobox, which encodes a 60 amino acid long DNA-binding protein domain, known as the homeodomain (6). Many homeobox-containing genes have been identified in invertebrates and vertebrates, including humans (6, 7). The main functions of non-homeotic homeobox genes include determining cell fate and differentiation pathways, and regulating the required cell behaviour during morphogenesis, such as migration (8).

Homeobox genes have been grouped into different classes and families. The human genome is estimated to contain around 235 functional homeobox genes (9). The *HOX* genes are a specific family of Homeobox-containing genes contained within four genomic clusters: these clusters are named A, B, C, and D and, based on sequence similarity, the genes are sorted into 13 paralogous groups with an equivalent position in each cluster. The genes are numbered in each cluster from 1 at the 3′ end to 13 at the 5′ end. When a paralogous group is absent from a cluster, the corresponding gene number is omitted (10). In humans, there are 39 *HOX* genes clustered on chromosomes 7p15.3, 17q21.3, 12q13.3, and 2q31 respectively (Figure 1) (11).

A number of associated molecular events are responsible for enhancement of homeodomain binding and specificity. Functional motifs contribute to homeodomain specificity by facilitating the interaction of *HOX* proteins with other transcription factors, such as PBX and MEIS (12, 13). *HOX*-PBX complexes have increased DNA binding affinity and specificity compared to *HOX* proteins alone (14, 15). With the aid of these co-factors, some *HOX* genes have distinct functions while many others appear to exhibit overlapping or redundant functions (16).

Regulation of *HOX* gene expression and activity

In development, the expression of *HOX* genes is highly organized along the antero-posterior axis in patterns termed spatial and temporal collinearity. In spatial collinearity, *HOX* genes toward the 3′ end of a cluster have a more anterior boundary of expression than those closer to the 5′ end. Thus, for example, the limit of *HOXB1* expression is at the midbrain/hindbrain border, whilst that of *HOXB9* is in the spinal cord. Temporal collinearity describes the correlation between the order and the timing of *HOX* gene expression during embryogenesis: early expression of 3′ genes during embryonic life versus the later expression of 5′ genes (17). In addition, *HOX* cluster genes exhibit "posterior prevalence", which is a functional dominance of posterior genes over their more anterior

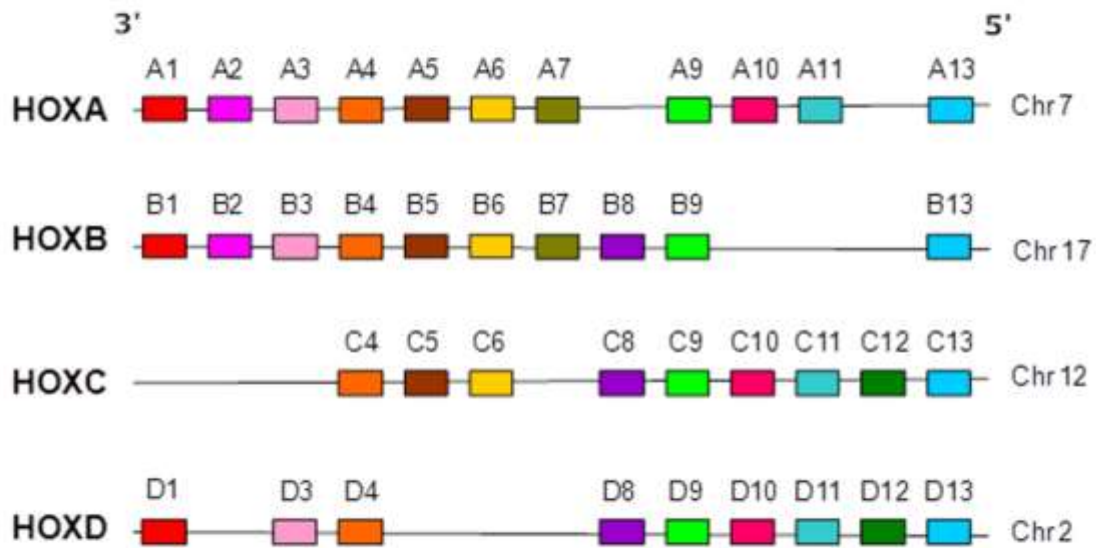

Figure 1. Diagram of the arrangement of HOX genes by paralogous group (1-13) in 4 clusters (A-D), each at a different chromosomal location.

neighbours (18). Other factors participate in the complex patterns of *HOX* gene expression and activation, including regulation during adulthood. These include hormones, such as oestrogen, progesterone (19-22) and retinoic acid (vitamin A) which is a key regulator of *HOX* gene expression during embryogenesis in a concentration-dependent manner (23-25).

There is also increasing interest in epigenetic control of *HOX* gene expression in the context of development and cancer. This includes co-ordinated changes in promoter methylation and histone modifications (26, 27). An overall screen of DNA methylation in oral cancer cells showed increased methylation at sites within the *HOX* clusters (28), and this was further explored in the *HOXB* cluster, with re-expression of *HOXB4* after treatment with DNA-methyl-transferase inhibitors (29). These changes have been linked to alterations in the activity of polycomb repressive complexes (PRCs) that can control *HOX* gene expression (30).

The *HOX* clusters also contain a number of short and long non-coding RNA transcripts (Figure 2). Some of these, for example miR-10 and miR-196, have been extensively investigated both in development and cancer, and have widespread effects, including repressing the expression of a number of *HOX* genes (31-34). miR-10b represses HOXD10 expression in breast cancer, contributing to enhanced migration and invasion via RhoA/RhoC signalling (35), although this effect is not seen in HNSCC (36). There is also accumulating evidence that a number of long non-coding RNAs, such as HOTAIR, have pro-tumourigenic effects in many cancers including HNSCC (37), some of which may be mediated by alterations in HOX gene expression and activity. The regulatory mechanisms of the HOX loci miRNAs generally remain unclear, although we have shown that miR196a can be expressed in a polycistronic transcript that includes HOXB9 and possibly other B cluster genes (32), which may indicate a direct link between the altered expression of HOX genes and their corresponding microRNAs in cancer.

***HOX* genes in human development**

It is widely accepted that during embryogenesis, *HOX* genes control the expression of development-associated genes via binding to regulatory elements in the DNA in order to regulate cellular proliferation, migration, and differentiation toward normal organogenesis and body axis patterning (35, 36). *HOX* proteins are essential for normal neuronal differentiation (37) and spinal cord formation (38), while others play key roles in the development of the gut (39), ear and hindbrain (40), limbs and vertebrae (41), skin (42), lungs (43), pancreas (44), reproductive organs (45) and vasculature (46). Moreover, *HOX* genes are necessary for normal hematopoietic development and differentiation, and are actively expressed in primary human stem/progenitor cells (47, 48).

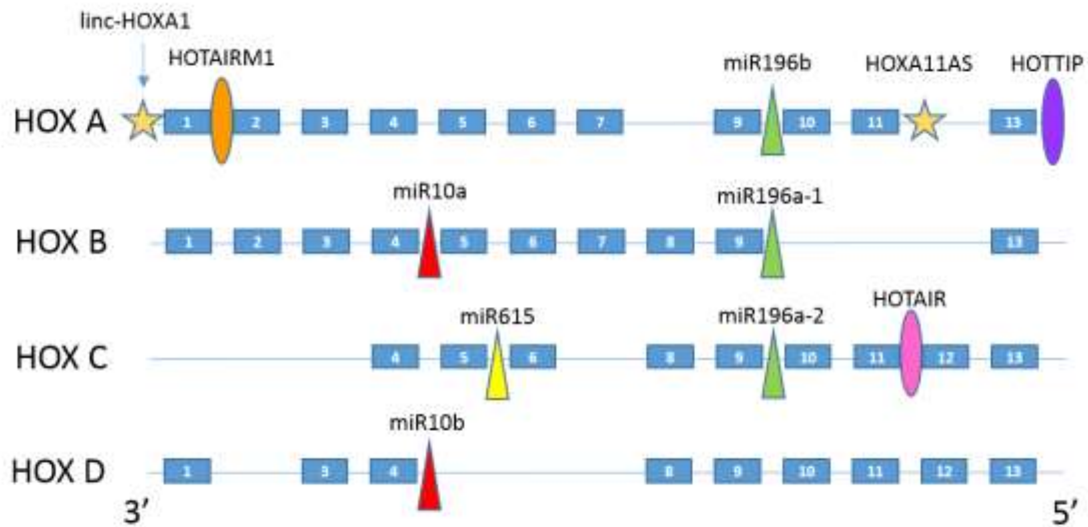

Figure 2. Schematic diagram of non-coding RNAs at their location within the HOX clusters. The HOX genes are shown as in Figure 1. A number of non-coding RNAs (both long and short) have been identified within the HOX clusters including micro-RNA families miR-196 (a-1, a-2 and b), and miR10 (a and b) and also miR615. Some have been shown to target genes within the HOX loci: miR10a targets HOXA1, HOXA3, HOXD10, miR10b targets HOXA1, HOXA3, HOXA11, HOXB3, HOXD10 and miR196b targets HOXB8. The long non-coding RNAs are linc-HOXA1 (which targets HOXA1), HOTAIR (HOX transcript antisense RNA: silences some HOXD genes), HOTAIRM1 (HOX antisense intergenic RNA myeloid 1), HOXA11AS (HOXA11 anti-sense: targets HOXA11), HOTTIP (HOXA Distal Transcript Antisense RNA: targets HOXA13).

Regulatory roles of *HOX* genes are not restricted to embryonic pattering since many of them are not only found to be detectable in embryonic tissues, but also in adult tissue in an organ-specific and collinear pattern of expression comparable to that of the developing embryo (49, 50). In particular, adult tissues with ongoing cell differentiation are often found to retain high expression of some *HOX* genes, for example *HOXA9*, *HOXA10*, *HOXA11*, and *HOXA13* expression in the male and female reproductive tracts helps to regulate spermatogenesis and endometrial remodelling (51, 52). Another example is hematopoietic stem cells, in which different combinations of *HOX* genes determine lineage identity and regulate cell proliferation (53). Furthermore, *HOX* genes are important players in some physiological processes such as wound healing (54), and lactation (55).

***HOX* genes and cancer**

Alterations in a number of *HOX* genes have been demonstrated in numerous types of cancer, but there is debate in the literature as to whether these are the cause or the effect of the malignant changes (56). An important point to note is that some members of the *HOX* gene family that have a pro-oncogenic role in one particular cancer may act as tumour suppressors in another cancer (56). A number of reasons for this have been suggested, including the presence or absence of some cofactors, in addition to variations in active pathways in different types of tissues (57). Moreover, such paradoxical observations support the concept that *HOX* gene activation and targets are cell and tissue type-specific. The underlying molecular mechanisms and the impact of abnormal *HOX* expression on the molecular pathology of different cancers remain elusive. However, the overall paradigm is that down-regulation or up-regulation of *HOX* genes lead to activation of embryonic developmental pathways in mature organs, thereby interrupting normal differentiation or cell growth pathways which in turn may contribute in abnormal cell behaviour and neoplasia (58, 59). In this regard, it is striking that the majority of up-regulated *HOX* genes in a cancer of a particular part of the body are normally expressed during development of that part, while the ones that are expressed normally in mature organs are down-regulated in cancer (56). Involvement of development-associated genes, such as *HOX* genes, in cancer gave rise to the "oncology recapitulates ontology" hypothesis (60, 61), which postulates that genes which determine the differentiation and lineage of the progenitor cells have important roles in cancer initiation. In general, abnormal changes in *HOX* gene expression have been found in a wide range of tumours and cancers, including leukaemia, breast cancer, prostate cancer, lung cancer and head and neck cancer (62-75). Selected findings are summarised in Table 1.

The importance of *HOX* genes in cancer biology is tightly linked to their capacity to regulate important mechanisms, such as angiogenesis, survival and apoptosis, cell proliferation, invasion, and

Cancer	**Changes in *HOX* genes reported**	**Clinical significance**	**References**
Leukaemia	Alterations mostly in A and B Cluster: *HOXA9*, *HOXA10* overexpression, *HOXA4*, *HOXA5* inactivation	High expression of *HOXA9* linked to poor prognosis in AML	65-67
Breast	*HOXA1*, A7, A5, and B7, expression, loss of *HOXA9* and *HOXD10*	*HOXB7* may confer chemotherapy resistance	68-71
Prostate	Reduced *HOXB13* and *HOXD10*. Varies by androgen dependency.	*HOXC6* and *HOXC8* may predict progression	72-75
Lung	*HOXA5 HOXA7*, *HOXA9 HOXA10* and *HOXB9* expression in NSCLC and SCLC, but some variation reported	*HOXA5* in SCLC linked to chemotherapy resistance	76-78

Table 1. Reported alterations in *HOX* gene expression in selected non-HNSCC cancers, demonstrating the wide range of *HOX* genes affected, some of which have proven clinical significance.

HOX gene	Source material	Alteration	Effect	Ref.
HOXA1	Oral cavity: tissues and cells	Increased expression in cancer	Promotes proliferation	93, 96
HOXA5	Oral Cavity: tissues	Increased expression in cancer	Not known	93
HOXA10	Oral cavity: cells and tissues	Increased expression in cancer	Not known	97
HOXB5	Oral cavity: tissues	Increased expression in cancer	Not known	99
HOXB7	Oral cavity: cells and tissues	Increased expression in cancer	Promotes proliferation	30, 93, 98
HOXB9	Oral cavity: cells and tissues	Increased expression in cancer	Promotes migration and proliferation	32, 93
HOXC5	Tongue: animal model tissues	Increased expression in cancer	Not known	101
HOXC6	Oral cavity: tissues	Increased expression in cancer	Associated with lymph node metastasis	93
HOXD10	Oral cavity: cells and tissues	High expression in primary tumour, reduced in metastases	Promotes proliferation and migration	36, 103

Table 2. The effects of alterations in *HOX* genes reported in HNSCC, with the source of the material used to generate the data.

metastasis (56). Given the involvement of *HOX* genes in such a wide range of developmental processes, it is unsurprising that they are also important in pro-tumourigenic processes, although their role in oncogenesis varies between cell and tumour types: thus, the context in which the altered expression occurs is crucial.

HOX genes promote terminal differentiation in some tumours, whilst conversely in others the expression of certain *HOX* genes is associated with the loss of terminal differentiation. For example, neuroblastoma cultures differentiate in the presence of various agents, such as retinoic acid and 5-bromo-2'-deoxyuridine, which may be due to the upregulation of specific *HOX* genes (76, 77). Contrastingly, overexpression of *HOX*C8 in prostate cancer cell lines is associated with loss of differentiation, and therefore promotes an oncogenic phenotype (70).

HOX genes also play important roles in cellular proliferation, and the overexpression of a number of *HOX*A and *HOX*B genes, including *HOX*A9, can promote the proliferation of haemopoietic stem cells in leukaemia (78). Upregulation of *HOX*A9 has been associated with the increased expression of insulin-like growth factor 1 receptor (IGF1R), which will increase autocrine stimulation (79).

HOX genes are directly involved with apoptotic pathways. *HOX*A5, in particular, has been linked with p53, as *HOX*A5 protein binds to the promoter region of TP53 to induce expression and subsequent p53-mediated apoptosis (80). Similarly, *HOX*A10 increases p53 expression in breast cancer cell lines (81). *HOX*A5 can also directly trigger apoptosis in breast cancer cells through the induction of caspases 2 and 8 (82). Conversely, *HOX* genes can, in some contexts, suppress apoptosis. This has been shown in non-small-cell lung cancer and some cases of melanoma (83, 84), where prevention of *HOX*-PBX dimerisation has resulted in increased apoptosis.

HOX genes have also been linked with Epithelial-Mesenchymal Transition (EMT) and invasion, and this is often associated with upregulation of *HOX* genes that are otherwise expressed at very low levels. For example, *HOX*B7 is overexpressed in breast cancer in both bone metastases and primary tumours. Cell line studies have shown that over-expression of *HOX*B7 can result in a metastatic phenotype, such as loss of adhesion and a number of morphological changes (85). Likewise, *HOX*B13 overexpression has been linked with cell invasiveness, proliferation and tamoxifen resistance in breast cancer (85).

***HOX* genes in head and neck cancer**

Over the last decade, the role of *HOX* genes in the development of HNSCC has been investigated by a number of research groups. These reports include the identification of groups of over-expressed *HOX* genes in a number of array-based HNSCC studies where normal oral mucosa and HNSCC were

compared (86-88). In these analyses, there are some alterations in *HOX* gene expression in common, but none of the findings are in complete agreement, as is often that case in array-based studies. Nevertheless, *HOX* genes do not rank highly in the majority of HNSCC transcriptome studies (including meta-analyses of such data: (89)). This might relate to a number of methodological factors including sample selection, methods of analysis and design of probesets.

The first complete expression profile of all 39 *HOX* genes in tissue samples of HNSCC, oral dysplasia and normal mucosa demonstrated that 18 of the 39 *HOX* genes had significantly increased expression in HNSCC when compared to normal tissues (90). The overexpressed genes were *HOX*A1, A2, A3, A5, A9, B3, B6, B7, B9, C4, C6, C8, C9, C11, C13, D9, D10 and D11. It should be noted that out of these 18 *HOX* genes, 11 were adjacent on the same cluster, which could indicate that *HOX* deregulation is controlled by common upstream regulators. Our *HOX* expression profile in normal, oral premalignant (OPML) and HNSCC cells showed that most of the *HOX* genes were more highly expressed in HNSCC cells compared to normal oral keratinocytes, some by 2-4 orders of magnitude (32). The differential expression was most marked for *HOXA4*, *HOXA5*, *HOXA9*, *HOXB9*, *HOXC9* and *HOXD10*. The expression of some *HOX* genes (B1, B8, C11, D3, D4, D11 and D12) was higher in normal oral epithelial cells than in oral cancer cells but, in general, these were expressed at a very low level. Rodini and co-workers identified 5 *HOX* genes that were overexpressed in HNSCC; these were *HOXA5*, A6, C9, D10 and D11 (91). From these, *HOXA*5, D10 and D11 were most highly expressed. Further investigation of these genes showed that high expression level of *HOXA5* was associated with favourable prognosis; patients with high *HOXA5* expression had an 83.3% survival rate, compared to 43% in patients who showed comparatively lower *HOXA5* expression. No such pattern was apparent for *HOXD10* or *HOXD11*. Similar to its role in breast cancer, *HOXA5* in HNSCC may act downstream of retinoic acid receptor, RARb, to promote retinoid-induced apoptosis and reduce cell survival (91). Thus overall screens of *HOX* gene expression in HNSCC have yielded overlapping patterns of alterations of *HOX* gene expression with some variation. This may be related to the type of analysis used, with those conducted in tissues reporting the closest patterns of expression.

HOX expression in HNSCC has also been compared in samples from patients with or without lymph node metastases. This revealed that expression of *HOXC5*, C6 and C8 were increased in the samples that had metastasised (90). Similar findings have also been presented in prostate cancer, showing that *HOXC4-6* were overexpressed in lymph node metastases compared to cancers from other sites and that human prostate cancer cell lines undergo apoptosis when small interfering RNAs (siRNAs) are used to inhibit *HOXC6* expression (92). It may therefore be the case that this region of the *HOX*C cluster is associated with a progressive cancer phenotype in both prostate cancer and HNSCC.

The *HOX* genes which have been individually investigated in HNSCC are summarised in Table 2, and are grouped according to the various clusters below.

***HOX*A cluster**

HOXA1 acts to increase cell proliferation as overexpression promoted proliferation and knock-down decreased proliferation of oral epithelial cells (93). Further investigation into other characteristics, such as apoptosis, adhesion, invasion and EMT markers found that *HOXA1* did not have a significant effect, however *HOXA1* overexpression was associated with lymph node metastasis and a lower overall survival rate. This finding in particular indicates that *HOXA1* may have potential as a prognostic marker (93).

HOXA10 expression has also been studied In HNSCC by Yamatoji and co-workers (94). Their findings suggest that *HOXA10* is overexpressed in HNSCC and associated with cancer stage, implying that its up-regulation may result in a disease progression. Furthermore, it was evident that *HOXA10* expression was related to survival. These results suggest that *HOXA10* could be used as a diagnostic and prognostic biomarker.

***HOX*B cluster**

Normal oral tissues generally do not express *HOXB* cluster genes, whereas HNSCC cells showed relatively high expression of *HOXB2*, *HOX*B5, *HOXB7* and *HOXB13* (95, 96). *HOXB7* is an important mediator of proliferation during development, and has been previously implicated to have a pro-oncogenic role in breast cancer and melanoma (95). Further experimentation showed that *HOXB7* overexpression was associated with proliferation of oral epithelial cells mediated by fibroblast growth factor (FGF). This has also been related to clinical behaviour, where a greater proportion of *HOX*B7-positive cells was associated with an aggressive cancer phenotype and lower survival rates.

Our recent study demonstrated overexpression of *HOXB9* in HNSCC (32). *HOXB9* is expressed early in embryogenesis, and overexpression has previously been implicated in breast cancer development (97). *miRNA-196a*, which is also highly expressed in HNSCC, is located immediately 5' of *HOX*B9 on chromosome 17 (Figure 2), suggesting that *HOXB9* and *miRNA-196a* could be co-regulated or expressed on a single polycistronic transcript. Reducing *HOXB9* expression in HNSCC cells decreased cell proliferation, migration and invasion (32).

***HOX*C cluster**

Increased expression of *HOXC5* has been correlated with proliferation and it is over-expressed in dysplastic and malignant cells in and oral carcinogenesis model (98). Interestingly, *HOXC5* expression was significantly higher in dysplastic lesions, as opposed to hyperplastic lesions, and the authors

suggest that *HOXC5* may serve as a useful early diagnosis biomarker to distinguish between hyperplastic and dysplastic lesions. This has considerable prognostic significance, as the majority of hyperplastic lesions do not progress to HNSCC (98). The same authors have reported overexpression of *HOXC6* in HNSCC tissues and cell lines, in which it regulated bcl-2 and was responsible for resistance to apoptosis (99).

***HOX*D cluster**

HOXD10 is overexpressed in some HNSCC cells, and some cell lines derived from OPMLs. This pattern was also seen in tissues, and *HOXD10* expression is reduced in cells from lymph node metastases, compared with their paired primary tumours (100, 101). When *HOXD10* expression was increased in low-expressing OPL and metastatic cells, there was a resultant increase in proliferation, migration and adhesion, but a decrease in invasion. Conversely, when *HOXD10* was knocked down in high-expressing HNSCC and OPML cells, this caused a decrease in proliferation, migration and adhesion, but an increase in invasion. This indicates that *HOXD10* may primarily be associated with development of the primary tumour, and that expression decreases as the cancer metastases. In fact, similar patterns of *HOXD10* expression have also been observed in bladder cancer (102) and breast cancer (103), however, as mentioned earlier, the functions of *HOX* genes are cell-specific so this may not be the case for all cancer types. The underlying mechanism for the down-regulation of *HOXD10* in HNSCC metastasis is unknown at present. Two novel targets of *HOXD10* were also identified. *miR-146a* is an inhibiter of proliferation and is down-regulated by *HOXD10*, whilst *AMOT-p80* expression is promoted by *HOXD10* and is associated with increased proliferation (100).

The mechanism of this widespread dysregulation of *HOX* genes in HNSCC has not been clearly established. The alterations in promoter methylation and histone modifications mentioned earlier play a role (28, 30), as do changes in microRNA expression, such as miR-196 (32, 104), and other transcription factors, such as POU2F1 (101). There are numerous reports of more widespread effects of alterations in the expression of miRNAs and lincRNAs encoded within the *HOX* gene cluster. Recently, both *miR10b* and *HOTAIR* have been implicated in the control of expression of E-cadherin and as such may have roles in the epithelial-mesenchymal transition in HNSCC (105). We have previously demonstrated in HNSCC that miR-196a inhibits HOXC8 expression (32), but, unlike that seen in breast cancer, miR-10b does not regulate HOXD10 in HNSCC (100).

The existence of *HOX* genes in clusters makes them particularly sensitive to changes in chromosomal organization, and activators of *HOX* transcription include genes that mediate this process, most notably the KMT2 (previously referred to as MLL) family of methyltransferases. KMT2 genes are amongst the most highly mutated in cancer, and have been shown to have oncogenic functions in a

wide range of solid malignancies including head and neck cancer (106, 107). These regulators also have crucial roles in normal development and haematopoiesis through the regulation of *HOX* genes. A number of studies demonstrated that KMT2-deficient embryonic bodies and conditional knockout mice showed a greatly reduced expression of a number of *HOX* genes including *HOX*A7, *HOX*A9 and *HOX*A10 as well as other *HOX*B and *HOX*C genes (108, 109).

The clinical utility of *HOX* genes in cancer

Given the high degree of *HOX* gene dysregulation seen in cancer, including very high expression of some in tissues, this raises the possibility of using *HOX* genes as biomarkers or targets for therapeutic intervention. Much work remains to be done before *HOX* genes could be utilised as biomarkers: and although changes in HOX expression have been linked with poor outcome in HNSCC (94, 110), it remains unclear how these alterations contribute to the natural history and clinical progression of HNSSC.

HOX genes do have potential advantages as therapeutic targets: the tumours arise in adult tissues, many of which no longer express *HOX* genes to any significant extent, which could confer a level of specificity not seen in other targeted therapies such as anti-EGFR therapy. However, the fact that similar/paralogous *HOX* genes often have overlapping functions makes it difficult to evaluate the effects of targeting individual genes and, indeed, to target specific genes. Indeed, it is likely that inhibition of all the genes within a particular paralogous group will be required. As an alternative approach, Morgan and co-workers developed the novel cell-permeable 18-amino acid peptide, HXR9, which competitively binds PBX by mimicking the hexapeptide sequence found in the *HOX* homeodomain, thus preventing many *HOX*-PBX interactions and repressing overall *HOX* gene function (111). *HOX*/PBX dimers have significantly greater binding affinity and specificity for target DNA sequences than the *HOX* monomer alone (112).

The effects of this peptide have been investigated in melanoma (111), non-small-cell lung cancer (NSCLC) (113) and prostate cancer (114). In all three of these studies, HXR9 resulted in increased apoptosis of cancer cell lines, believed to be partially due to increased translation of cFos. cFos has been previously shown to repress c-FLIP(L), a gene with anti-apoptotic functions, thus sensitising cancer cells to apoptosis (115). For NSCLC cells, exposure to HXR9 was also associated with an increase in expression of the early growth response 1 (EGR1) gene, which is known to prevent angiogenesis and tumour invasion while promoting apoptosis (113). Prostate cancer cell lines, which showed dysregulated *HOX* expression, were more sensitive to HXR9-induced cell death than a cell line derived from normal tissue (116). The effects of HXR9 *in vivo* were compared to a control peptide, CXR9, which does not have a functional hexapeptide sequence, by injection into murine

models of prostate cancer. After 52 days the tumours treated with CXR9 had increased size by 8 fold, compared to a 1.5 fold increase for the HXR9-treated tumours. Histological examination found that CXR9-treated tumours were composed mainly of undifferentiated cells, whereas the HXR9-treated tumours had relatively few cells and were composed mainly of cellular debris (116). A similar method was used to investigate NSCLC and melanoma, with similar results of reduced tumour growth and increased cell death. Given this data in a number of tumour types, there is a substantial body of evidence that targeting *HOX*-PBX interactions could pose a viable therapeutic strategy. We are currently evaluating these effects of these peptides in HNSCC cells

There are, however, a number of limitations to this approach. These include lack of specificity and the observation that 5' *HOX* genes, many of which are highly expressed in cancer, are less PBX dependant. Some of these may be more dependent on MEIS as a cofactor. Other possible approaches include the introduction of *HOX*-specific siRNA or shRNA capable of reducing the expression of cancer-promoting *HOX* genes or by the re-expression of tumour suppressing *HOX* genes. This method has been successful in previous studies, where re-introduction of *HOX*D10 suppressed the growth and progression of metastatic breast cancer cells (117).

Conclusion

It is clear that *HOX* genes play an important role in the oncogenesis and metastasis in many cancers, including HNSCC. Genes of specific note have been discussed, however targeting individual *HOX* genes may not be a viable therapeutic option due to the functional redundancy of many *HOX* members. There are a number of outstanding questions which require an answer before their potential can be fully assessed, however their dysregulation in this malignancy suggests that they could act as key prognostic and diagnostic markers, as well as therapeutic targets. However, further study is necessary before the clinical utility of this approach can be established and we are currently pursuing a number of these outstanding issues in an attempt to understand the biology and clinical utility of *HOX* genes in HNSCC.

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