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Homeobox gene expression in cancer: Insights from developmental regulation and deregulation

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Abstract

Homeobox genes encode transcription factors that play essential roles in controlling cell growth and differentiation during embryonic development. Many homeobox genes are aberrantly expressed in a wide variety of solid tumours, and their deregulation appears to enhance cell survival and proliferation and to inhibit differentiation. In hematologic malignancies, deregulated homeobox genes profoundly perturb self-renewal and proliferation of hematopoietic stem cells and progenitors. It is increasingly recognised that solid tumours, like hematologic malignancies, could arise from cancer stem cells, and that targeting these cells could be the most effective means of inhibiting tumour progression and disease recurrence. Studying the biological effects and mechanisms of homeobox genes in cancers could provide valuable insights into identifying cancer stem cells and targeting the self-renewal pathways in these cell populations.

Keywords: Homeobox genes; Embryonic patterning; Differentiation; Neoplastic transformation; Self-renewal

1. Homeobox genes are master regulators of developmental patterning

Homeobox genes constitute a superfamily of genes that control cell differentiation and morphogenesis during embryonic development. These "master-regulatory" genes are characterised by the presence of a signature DNA sequence that encodes a 61 amino acid domain known as the homeodomain (Fig. 1). Homeodomains form a helix-turn-helix motif that binds sequence-specific DNA elements. Proteins encoded by homeobox genes function as transcription factors that activate or repress the expression of batteries of downstream target genes [1]. Homeobox genes were first discovered in the fruit fly *Drosophila* as genes whose mutations caused homeotic transformation, *i.e.*, formation of body segments in an inappropriate location or context. One well-studied example of a homeotic transformation in *Drosophila* is the formation of additional legs rather than antennae in gain-of-function mutants of the *Antennapedia* gene. In loss-of-function mutants of the *Ultrabithorax* gene, the normally wingless third thoracic segment is transformed into a second thoracic segment with wings, thus resulting in four-winged flies (reviewed in [2,3]).

Homeobox genes are highly conserved throughout evolution and are categorised into several families. Members of the *Drosophila HOM-C* family, the prototype homeobox genes that include *Ultrabithorax* and *Antennapedia,* are clustered. The counterpart in mammals, the *HOX* family, comprises 39 genes that are tandemly arranged in four clusters located on different chromosomes, and are thought to have arisen by duplication and divergence from a primordial *HOX* gene cluster [4,5]. Based on their sequence similarities and relative positions in the loci, *HOX* genes within the

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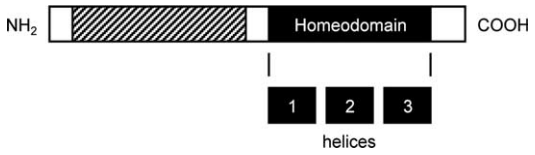

Fig. 1. Structure of a prototype homeoprotein. Homeobox genes are characterised by a 183 bp DNA sequence (the homeobox) that encodes a 61 amino acid domain (the homeodomain). The three-dimensional structure of the homeodomain corresponds to three alpha-helices that bind specific DNA elements, primarily those that contain a TAAT core motif. Homeobox genes are categorised into families based on sequence similarities of their respective homeodomains and additional conserved domains. Members of the *SIX*, *PAX*, *LIM* and *MSX* families contain additional conserved domains within their amino-terminal regions. Members of the *HOX* family contain a short conserved motif adjacent to the homeodomain that permits binding of co-factors such as PBX and MEIS. The sequence diversity among homeoproteins is thought to generate different DNA-binding specificities and promote unique protein–protein interactions that contribute to the distinct functional properties of homeoproteins.

different clusters are aligned with each other and with genes of the *Drosophila HOM-C* cluster in 13 paralogous groups. The spatial and temporal expression of *HOX* genes along the anterior–posterior axis during embryonic development is tightly coupled to their physical organisation [4,5]. *HOX* genes at the 3′ end of the clusters are generally expressed early in development and in anterior regions, whereas those at the 5′ end of clusters are expressed later and in more posterior regions. Recently, a new cluster of twelve related homeobox genes, termed *Rhox* genes, was discovered on the mouse X-chromosome [6]. Other vertebrate homeobox gene families consist of two-to-nine members that are dispersed throughout the genome and are named after their homologs in the fly. Some of these include the *Dlx (Distal-less)*, *Msx (muscle segment)*, *Pax (paired)*, *Cdx (caudal)*, *EN (Engrailed)*, *Emx (empty spiracles)* and *Otx (orthodenticle)* families.

Loss- and gain- of function analyses have revealed that the vertebrate homeobox gene network regulates a broad spectrum of biological functions during embryonic development. These include limb formation, axial skeleton patterning, craniofacial morphogenesis, development of the central nervous system, and organogenesis including development of the gastrointestinal tract and reproductive organs [4,5,7]. Furthermore, specific sets of homeobox genes regulate reproductive function in the adult [7], angiogenesis [8] and, as discussed later, hematopoiesis.

2. Spectrum of deregulated homeobox genes in cancers

It is widely accepted that the processes of normal embryogenesis and neoplasia share many of the same pathways, and that tumour development is an aberrant form of organogenesis. Several important pathways that control pattern formation and pattern maintenance, such as the Wnt and Hedgehog signalling pathways, are deregulated in various cancers such as colorectal cancer, basal-cell carcinoma and medulloblastoma, and their deregulation significantly contributes to the pathobiology of these diseases (reviewed in [9,10]). Homeobox genes represent classic examples of the intimate relationship between embryogenesis and neoplasia. Increasing numbers of homeobox genes have been found to be aberrantly expressed in a variety of solid tumours (reviewed in [11–13]), and several representative examples of these deregulated genes are listed in Table 1.

Aberrant expression of homeobox genes also frequently occurs in hematologic malignancies [14–17]. In many instances, this deregulation is attributed to chromosomal translocations (Table 2). One well-characterised example is the t(7;11)(p15;p15) translocation in acute myeloid leukemia (AML) that results in a chimeric oncoprotein containing the amino-terminal region of the nuclear pore complex protein NUP98 fused to the HOXA9 protein [18,19]. Fusion of NUP98 to various other homeoproteins arising from chromosomal translocation has also been reported, and some examples of these are listed in Table 2. Deregulation of homeobox genes through translocations also occurs in sarcomas. In alveolar rhabdomyosarcoma, translocations result in the fusion of DNA-binding regions of PAX3 and of PAX7 to the FKHR transcription factor [20,21]. Several homeobox genes localise to "hotspots" that undergo loss of heterozygosity (LOH) in cancers such as the *NKX3.1* gene that maps to 8p21, a region that is deleted in approximately 80% of prostate cancers [22]. This region also frequently undergoes allelic loss in pre-cancerous lesions of the prostatic epithelium termed prostatic intraepithelial neoplasia (PIN) [23]. The *BARX2* and *CUTL1* genes localise to regions that are frequently deleted in ovarian cancers and in uterine leiomyomas, respectively [24,25]. Epigenetic mechanisms also contribute to deregulated homeobox gene expression in cancers. Loss of *HOXA5* expression occurs in >60% of breast cancers, and is associated with methylation of the *HOXA5* promoter [26].

3. Tumour-suppressing effects of homeobox genes

Although increasing numbers of homeobox genes have been reported to be aberrantly expressed in solid tumours during the past two decades, the functional significance of their deregulation has only gained considerable attention in recent years and for many of these genes has yet to be precisely defined. From the functional studies to date, two broad trends of homeobox gene expression in solid tumours and the overall consequences of this deregulation have emerged. In the first category are homeobox genes whose expression is downregulated or lost in

Table 1
Examples of aberrantly expressed homeobox genes in solid tumours

Gene	Expression pattern	Functional insights	References
Downregulated genes			
NKX3.1	Expressed during normal prostate development and in adulthood. Maps to chromosomal region 8p21 which frequently undergoes LOH in PIN and in prostate cancer	Homozygous and heterozygous *Nkx3.1* mutant mice develop PIN. Loss of function of *Nkx3.1* and *Pten* cooperate to induce prostate cancer. Ectopic *Nkx3.1* expression in prostate cancer cell lines suppresses growth	[22,23,27–30]
CDX2	Expressed during normal gut development and in adulthood. Loss of expression in colorectal cancers correlates with promoter methylation	Heterozygous *Cdx2* mutant mice develop intestinal adenomatous polyps and are more susceptible to undergo chemically induced colon carcinogenesis than wild-type mice Ectopic *Cdx2* expression in colon cancer cell lines suppresses growth	[31–35,81]
HOXA5	Loss of expression occurs in >60% of breast cancers and correlates with promoter methylation	Loss of *HOXA5* expression correlates with loss of p53 expression. HOXA5 is a transactivator of the *p53* promoter	[26]
BARX2	Expressed in normal ovarian surface epithelium. Maps to chromosomal region 11q24-q25 which frequently undergoes LOH in ovarian carcinoma	Ectopic *BARX2* expression in ovarian carcinoma cell lines suppresses invasive behaviour and increases sensitivity to cisplatin	[24,82]
CUTLI	Maps to chromosomal region 7q22 which frequently undergoes LOH in uterine leiomyomas and breast cancers		[25,83]
LAGY	Expressed in normal brain, heart, skeletal muscle, placenta and lung. Downregulated in lung cancers. Maps to 4ql1-13.1 region that is frequently deleted in lung tumours		[84]
HOXC4	Expressed in normal skin keratinocytes. Downregulation in epidermal tumours correlates with loss of differentiation		[85]
NKX6B	Highly expressed in normal brain. Maps to chromosomal region 10q26 which frequently undergoes LOH in brain tumours		[86]
ALX3	Highly expressed in normal brain. Loss of expression in neuroblastomas correlates with promoter methylation		[87]
Upregulated genes			
HOXA1	Expressed in neoplastic but not in normal mammary tissues	Ectopic *HOXA1* expression in immortalised breast epithelial cells induces oncogenic transformation and, in breast cancer cells, promotes survival by upregulating bcl-2 expression	[41,42]
HOXA7	Not expressed in normal ovarian surface epithelium and activated in differentiated epithelial ovarian tumours	Ectopic *HOXA7* expression in immortalised ovarian surface epithelial cells induces mesenchymal-to-epithelial transition and, in transformed ovarian surface epithelial cells, induces formation of low grade tumours	[88,89]
HOXC8	Overexpression in prostate cancers correlates with loss of tumour differentiation	Overexpression of *HOXC8* in prostate cancer cells suppresses androgen receptor-mediated transcription	[90,91]
MSX1	Expressed in various embryonic tissues including the developing mammary buds	Transgenic mice overexpressing *Msx1* in the mammary gland exhibit impaired mammary epithelial differentiation that is associated with increased *cyclin DI* expression. Ectopic *Msx1* expression in myoblasts inhibits terminal differentiation and induces transformation	[40,50]
PAX2	Expressed during embryonic urogenital development. Expressed in Wilms' tumours, renal cell carcinomas, polycystic kidneys and in several other types of cancers	Reduced *Pax2* gene dosage in a mouse model of polycystic kidney disease increases apoptosis and slows disease progression Silencing of *PAX2* expression in various cancer cell lines induces apoptosis	[43,45–48]

Table 1 (*continued*)

Gene	Expression pattern	Functional insights	References
HSIX1	Overexpressed in primary and metastatic breast cancers as compared with normal mammary tissue. Expression in rhabdomyosarcomas correlates with clinical stage	Overexpression of *HSIX1* in breast cancer cells abrogates the DNA damage-induced G_2 cell cycle checkpoint, and activates cyclin Al expression. Overexpression in rhabdomyosarcoma cells increases metastatic behaviour	[53,54,92]
HOXB7	Overexpressed in breast and ovarian cancers and melanomas	Growth-promoting effects of *HOXB7* in breast cancer cells, ovarian surface epithelial cells and melanomas is associated with upregulated basic fibroblast growth factor expression	[93–95]
GBX2	Overexpressed in prostate cancer as compared with normal prostate epithelium	Downregulating *GBX2* expression in prostate cancer cells inhibits tumourigenicity, and correlates with decreased IL-6 expression	[96,97]
Nanog	Highly expressed in embryonic stem (ES) cells, and downregulated during ES cell differentiation. Undetectable in most normal adult tissues. Expressed in testicular carcinoma *in situ* and germ cell tumours	*Nanog* maintains pluripotency of ES cells and can maintain self-renewal of ES cells independently of LlF/Stat3	[98–100]
DLX4(BP1) and DLX7	Splice variants of the same transcript. Frequently co-expressed in AML. Activation of *BP1* in breast cancers correlates with disease progression	Apoptosis is induced following inhibition of *DLX4* expression in choriocarcinoma cells and of *DLX7* expression in erythroleukemia	[101–104]

Table 2
Examples of chromosomal aberrations resulting in deregulated homeobox gene expression in leukemias

Chromosomal rearrangement	Chimera	Expression	References
Translocation-induced fusion			
[t(7;11)(p15;p15)]	*NUP98-HOXA9*	Predominantly occurs in AML. Also occurs in CML and MDS	[18,19,105,106]
[t(7;11)(p15;p15)]	*NUP98-HOXA11*	Originally identified in CML	[107]
[t(7;11)(p15;p15)]	*NUP98-HOXA13*	Originally identified in MDS	[107]
[t(11;12)(p15;q13)]	*NUP98-HOXC11*	Originally identified in AML	[108]
[t(2;11)(q31;p15)]	*NUP98-HOXD11*	Originally identified in AML	[109]
[t(2;11)(q31;p15)]	*NUP98-HOXD13*	Originally identified in therapy-related AML,	[110]
[t(1;19)(q23;p13.3)]	*E2A-PBX1*	Occurs in pre-B ALL	[111]
Chromosomal rearrangement	**Gene activated**	**Expression**	**References**
Inversion-induced activation			
[inv[7](p15q34)]	*HOXA10*	T-ALL	[112]
[inv[7](p15q34)]	*HOXA11*	T-ALL	[112]

Abbreviations used: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome.

tumours (Table 1). Many homeobox genes that fall in this category are normally upregulated during embryonic development and their expression is maintained in fully differentiated adult tissues. One example is *Nkx3.1*. This homeobox gene is expressed from the earliest stages of prostate development to adulthood, and regulates differentiation of the prostatic epithelium [27]. Homozygous and heterozygous *Nkx3.1* mutant mice develop PIN, but these lesions do not progress to carcinoma [27,28]. However, inactivation of *Nkx3.1* in mice cooperates with loss-of-function of the *Pten* tumour suppressor gene to induce carcinoma [29]. Furthermore, overexpressing *Nkx3.1* in prostate carcinoma cells inhibits its growth *in vitro* and in nude mice [30].

A strikingly similar example of loss-of-function of a homeobox gene is *CDX2*. *CDX2* controls differentiation of intestinal epithelium and is normally expressed in the gut during development and in the adult [31]. Expression of CDX2 protein is reduced in colorectal tumours, particularly in high-grade carcinomas [32], and ectopically expressing *CDX2* in colorectal cancer cell lines inhibits cell growth [33]. *Cdx2* heterozygous mutant mice develop adenomatous intestinal polyps, but not spontaneous malignant tumours [34]. However, inactivation of *Cdx2* enhances the sensitivity of mice to chemically induced colon carcinogenesis [35].

The implication that arises from the studies of *Nkx3.1* and *Cdx2* is that loss of function of a homeobox gene that is normally expressed in a differentiated adult tissue and that specifies its identity is alone insufficient to induce malignancy. However, this loss appears to drive cells back to a less differentiated, highly proliferative

state and predisposes or primes a cell for neoplastic transformation. One primary mechanism by which homeobox genes exert this effect is by deregulating expression of components of the cell cycle machinery [11,36]. An example is the *p21* gene that is transcriptionally activated by several homeodomain-containing factors including CDX2 [37]. Loss of expression of *HOXA5* in breast cancers correlates with loss of p53 expression, and HOXA5 has been found to activate the promoter of the *p53* gene [26].

4. "Tumour-promoting" effects of homeobox genes

In the second broad category are homeobox genes that are overexpressed or aberrantly activated in solid tumours (Table 1). The frequent detection of upregulated homeobox gene expression in tumours prompted considerable early speculation that these genes could function as oncogenes. Several members of the *PAX* and *HOX* gene families have been reported to transform rodent fibroblasts [38,39]. However, the transforming ability of homeobox genes has been demonstrated in very few other cell types. One notable example is the *Msx1* gene that blocks terminal differentiation and induces transformation when ectopically expressed in myoblasts [40]. Another example is *HOXA1*. This *HOX* gene is expressed in neoplastic but not in normal mammary tissues [41]. Ectopic expression of *HOXA1* in immortalised breast epithelial cells induces malignant transformation, and promotes survival of breast cancer cells by upregulating bcl-2 expression [42]. However, the possibility that most homeobox genes that are aberrantly activated in tumours can act as *bona fide* oncogenes remains controversial because their oncogenic potential has not been conclusively demonstrated in normal cells from which the tumours arise.

Many of the homeobox genes that are normally expressed by embryonic tissues are aberrantly activated or "re-expressed" in tumours (Table 1). The *Pax2* homeobox gene is expressed in both ductal and mesenchymal components that derive from the intermediate mesoderm during development of the pronephros, mesonephros and metanephros [43]. Recently, a subpopulation of *PAX2*-expressing $CD133^+$ cells, isolated from normal adult human kidney, was found to possess self-renewal capability and proliferative and differentiative potential, indicating that this subpopulation represents renal progenitor cells [44]. *PAX2* expression is widely detected in Wilms' tumour, renal cell carcinoma and polycystic kidneys [45–47]. Reducing *Pax2* gene dosage in a mouse model of polycystic kidney disease has been found to increase cell death and slow disease progression [47]. In addition, silencing of *PAX2* expression in various human cancer cell lines induces apoptosis [48]. Together, these findings suggest that overexpression of *PAX2* in tumours maintains an undifferentiated, proliferative state, enhances cell survival and/or promotes self-renewal.

Several other overexpressed homeobox genes have been found to inhibit differentiation and to promote cell growth. *Msx1* is normally expressed in a wide range of embryonic tissues including the developing mammary buds [49]. Mammary epithelial differentiation is inhibited in transgenic mice overexpressing *Msx1* in the mammary gland, and this inhibition is associated with upregulation of *cyclin D1* expression [50]. The ability of *Msx1* to block differentiation of myoblasts is also associated with its upregulation of *cyclin D1* [50]. Members of the *Six* homeobox gene family are also expressed in a variety of embryonic tissues [51,52]. Overexpression of *HSIX1* occurs in 44% of primary breast cancers and 90% of metastatic tumours, and abrogates irradiation-induced G2 cell cycle arrest [53]. Overexpression of this homeobox gene is thought to reinstate an embryonic pathway of proliferation in breast cancers by upregulating cyclin A1, a tissue-restricted cyclin that is expressed in the embryonic mammary gland but not in the differentiated adult gland [54].

The studies discussed above indicate that homeobox genes that are lost or downregulated in cancers do not act as classical tumour suppressors. Conversely, it remains controversial as to whether homeobox genes that are overexpressed in tumours function as *bona fide* oncogenes. What emerges from the studies is that the down- or upregulation, depending on the individual homeobox gene, profoundly alters cell phenotype and behaviour, and that the overall functional consequences of the aberrant expression are remarkably similar. These include reverting cells to a less differentiated, embryonic-like state, promoting survival and enhancing proliferation, and these alterations increase predisposition to neoplastic transformation and/or promote tumour progression.

5. Promotion of stem cell renewal by homeobox genes

During the past 15 years, it has become clear that homeobox genes not only control organogenesis and body formation during embryonic development, but also play significant roles in regulating hematopoiesis. A number of studies have shown that *HOX* genes are expressed in hematopoietic cells in a stage- and lineage-specific manner. Many of the genes in the *HOXA*, *HOXB* and *HOXC* clusters, but not the *HOXD* genes, are expressed by different subpopulations of $CD34^+$ bone marrow cells [55,56]. *HOXA* and *HOXB* genes located at the 3′ ends of the clusters tend to be preferentially expressed by the most primitive hematopoietic stem cells (HSCs), whereas genes located at the 5′ end

tend to be expressed in myeloid and erythroid progenitors [55,56].

The distinct stage- and lineage-specific expression patterns of *HOX* genes in normal hematopoietic cells reflect their distinct functions. Much of our understanding of the functions of *HOX* genes in hematopoiesis has come from studies in which *HOX*-transduced primary murine bone marrow cells have been transplanted into recipient mice (reviewed in [12,14–16]). These investigations and studies from knockout mouse models have revealed that deregulation of specific sets of *HOX* genes profoundly perturbs self-renewal and proliferation of primitive HSCs and also expansion of progenitors of distinct cell lineages. Several of these studies are summarised in Table 3.

Overexpression of several *HOX* genes has been found to induce leukemogenesis. One example is *HOXA10*, which is widely expressed in AML [57]. Overexpression of *HOXA10* in mouse bone marrow cells has been found to block B-cell development and to promote expansion of progenitors with megakaryocytic colony-forming ability [58]. Moreover, mice transplanted with *HOXA10*-transduced bone marrow cells developed AML [58]. However, the latency period of 5–12 months indicated that the cooperative effect of other factors is required for accelerated leukemogenesis. Members of the *HOX* family contain a motif adjacent to the homeodomain that permits binding of cofactors such as PBX and MEIS proteins (Fig. 1). *HOXA9* expression is the single most highly correlated factor with poor prognosis in AML patients, and *HOXA9* is frequently co-expressed with *MEIS1* [59,60]. *Hoxa9* has been found to transform primary mouse bone marrow cells in collaboration with *Meis1a* [61]. Mice transplanted with bone marrow cells transduced with a combination of *Hoxa9* and *Meis1a* developed AML in <3 months [61]. In contrast, mice reconstituted with bone marrow cells expressing *Hoxa9* alone developed AML only after a latency period of 6–8 months and no tumour formation was observed within this period with *Meis1a* alone. *HOXB3* also collaborates with *MEIS1* to induce AML in mice [62]. However, not all *HOX* genes induce leukemogenesis. *HOXB4* promotes regeneration of primitive HSCs without altering their pluripotency [63], but mice transplanted with *HOXB4*-transduced bone marrow cells do not develop leukemia [58]. Exploiting this property of *HOXB4* has been explored as a potentially harmless

Table 3
Hematopoietic phenotypes resulting from *Hox* gene deregulation in mice

Gene	Phenotype	References
Hox gene overexpression		
Hoxb3	Disrupted T and B cell differentiation. Increased granulopoiesis. Development of myeloproliferative disorder	[113]
Hoxb4	Promotes regeneration of primitive HSCs without affecting pluripotency	[63,114]
Hoxb6	Expansion of HSCs and myeloid precursors. Impaired erythropoiesis and lymphopoiesis. Development of AML after latency period of 7–8 months	[115]
Hoxb8	Enhances self-renewal of immature myeloid progenitors and blocks differentiation of factor-dependent myeloid progenitors	[116,117]
Hoxa9	Immortalises and blocks differentiation of factor-dependent myelomonocytic progenitors. Collaborates with *Meis1a* to transform bone marrow cells and induce AML after latency period of < 3 months	[61,118]
Hoxa10	Disrupts B cell development. Increase in progenitors with megakaryocyte colony-forming ability. Development of AML after latency period of 5–12 months	[58]
Targeted disruption of *Hox* genes		
Hoxb4	Reduction in HSC pool in bone marrow and fetal liver, without perturbing differentiative potential	[119]
Hoxb6	Increased number of erythroid progenitors in bone marrow and fetal liver. Differentiation of other cell lineages unaffected	[120]
Hoxc8	Reduction in number of erythroid and granulocyte/macrophage progenitors in fetal liver	[121]
Hoxa9	Reduction in numbers of myeloid, erythroid and pre-B progenitors in bone marrow, and of granulocytes and lymphocytes in peripheral blood. Induction of apoptosis in primitive thymocytes	[122,123]

approach of *ex vivo* expansion of human HSCs for therapeutic purposes [64].

As is the case in hematopoiesis, other normal organs originate from a tissue stem cell, and evolve and regenerate by a developmental hierarchy. Normal stem cells are characterised by their self-renewal capability, potential to undergo extensive proliferation, and multipotency. Because tumour development is an aberrant form of organogenesis, a picture has emerged in which tumours have a similar hierarchical development as their normal tissue counterparts. The existence of cancer stem cells was originally demonstrated in the context of AML, and leukemic stem cells have been found to retain many of the characteristics of normal HSCs [65,66]. Solid tumours are increasingly thought to arise from maturation arrest of a cellular lineage derived from a small population of stem cells that exist in adult tissues (reviewed in [67–69]). Cancer stem cells have been identified in tumours that arise from various organ sites such as breast, brain and ovary [70–72]. One question that remains subject to debate is whether cancer stem cells truly arise by mutational transformation of normal stem cells, or could arise from restricted progenitors or even differentiated cells that upon mutational transformation acquire stem cell-like properties.

The view that cancer is a disease driven by a minority population of cancer stem cells has been dramatically shaped by studies of the Wnt, Hedgehog, Polycomb and Notch signalling pathways, which are expertly reviewed elsewhere [9,10,67,68]. These pathways control self-renewal of stem cells in a wide variety of organ systems including the hematopoietic system, and deregulation of these pathways has emerged as driving forces of tumour pathogenesis. As discussed above, homeobox genes have also been implicated in regulating self-renewal and expansion of stem cells and progenitors during embryonic development and in hematopoiesis. There is considerable evidence that *HOX* genes are regulated by *Polycomb* genes [73–75]. In addition, cross-regulatory interactions have been reported between various homeobox genes and the Wnt, Hedgehog and Notch signalling pathways [76–79]. Thus, it is highly likely that homeobox genes form important hubs in the network of self-renewal programs in normal organs and in tumours.

6. Conclusion

The possibility that cancers arise from cancer stem cells has profound implications for therapy. Existing anti-cancer therapies have been mostly developed against the bulk population of tumour cells. Although high initial response rates have been achieved by many regimens, these have not translated into high cure rates. For many years, the failure of therapies has been attributed to the acquisition of drug resistance by tumour cells. However, it is increasingly thought that disease recurrence could also be due to the failure of existing therapies to effectively eradicate the small population of cancer stem cells [80]. Targeting cancer stem cells represents a potentially effective means of inhibiting tumour progression and disease recurrence, but this approach requires the ability to block the self-renewal capability of a small population of cancer stem cells without toxicity to normal stem cells. It is possible that distinct sets of homeobox genes could control self-renewal of cancer stem cells in solid tumours and in hematologic malignancies. Future studies of the functional roles and mechanisms of homeobox genes in cancers should provide valuable insights into identifying cancer stem cells, and elucidating means to effectively target self-renewal pathways in these cell populations.

Conflict of interest statement

None declared.

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