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Review

HOXA1, a breast cancer oncogene

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ABSTRACT

More than 25 years ago, the first literature records mentioned *HOXA1* expression in human breast cancer. A few years later, *HOXA1* was confirmed as a proper oncogene in mammary tissue. In the following two decades, molecular data about the mode of action of the HOXA1 protein, the factors contributing to activate and maintain *HOXA1* gene expression and the identity of its target genes have accumulated and provide a wider view on the association of this transcription factor to breast oncogenesis. Large-scale transcriptomic data gathered from wide cohorts of patients further allowed refining the relationship between breast cancer type and *HOXA1* expression. Several recent reports have reviewed the connection between cancer hallmarks and the biology of *HOX* genes in general. Here we take HOXA1 as a paradigm and propose an extensive overview of the molecular data centered on this oncoprotein, from what its expression modulators, to the interactors contributing to its oncogenic activities, and to the pathways and genes it controls. The data converge to an intricate picture that answers questions on the multi-modality of its oncogene activities, point towards better understanding of breast cancer aetiology and thereby provides an appraisal for treatment opportunities.

1. Introduction

The breast is a glandular organ that evolves dramatically during a woman's life, from embryo to menopause with major changes during puberty and pregnancy. Cell heterogeneity and plasticity, as well as the frequent remodelling of the entire mammary gland, with repeated proliferation-apoptosis cycles, sow the seeds for cell cycle deregulation and mutation events, and finally for tumour development [1–4]. Breast cancer is the most diagnosed and leading cause of cancer mortality in women worldwide [5]. Breast cancers have been classified into four commonly accepted molecular subtypes: luminal A, luminal B, HER2-enriched and basal-like tumours. This classification is originally based on the expression status of three markers – estrogen receptor (ER), progesterone receptor (PR) and tyrosine kinase receptor HER2 – and was subsequently completed by transcriptomic data analysis [6–9]. Luminal A are ER-positive, PR-positive and HER2-negative tumours. Luminal B tumours are also positive for hormone receptors but can be either positive or negative for HER2 expression. HER2-enriched cancers are negative for ER and PR and show high-level HER2 expression. Basal-like subtype tumours are negative for all three markers. The correspondence between triple-negative breast cancers (TNBCs) and basal-like cancers is still under debate, since all TNBCs do not share basal-like features [10].

Luminal subtype tumours, that express ERα, account for around 70% of breast cancers [8]. ERα belongs to the large Nuclear Hormone Receptor (NHR) family and is a transcription factor that mediates the mitogenic action of estrogens, essential for mammary gland development. Therefore, modifications in its abundance, stability or degradation, lead to cell physiology changes and eventually to breast cancer emergence [11–13].

Because of the predominance of ER-positive breast cancers, major efforts were aimed at the development of endocrine therapy, to block ERα-mediated tumour progression. Endocrine therapies encompass aromatase inhibitors, selective ER modulators (SERMs) and selective ER downregulators (SERDs). Tamoxifen was the first and still is the most common SERM. It has been used in the clinic since the 1970's, and remains the gold standard in ER-positive breast cancer therapy [14]. As Tamoxifen resistance occurs in about 30% of ER-positive breast cancer patients, elucidating the molecular mechanisms and environment that

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contribute to therapy failure is an important research field [15–20]. One approach to better understand therapy resistance is to investigate other oncogenes and their relationships with ERα. Like other well-studied players such as HER2 or NF-κB, HOX proteins have emerged as important oncogenesis protagonists, as oncogenes or, inversely, as tumour suppressors [21–23]. Several *HOX* oncogenes were shown to functionally interact with ERα and to be involved in endocrine therapy resistance [21,23,24]. In the late 90's, expression of *HOXA1* was reported in breast cancers [25], and a few years later it was confirmed as a breast cancer oncogene [26]. In almost two decades, functional data have accumulated about the mode of action of *HOXA1,* and its expression in breast tumours has been confirmed in multiple breast cancer transcriptome datasets. In this paper, we will extensively review what has been published in the literature about *HOXA1* regulation and activity in breast cancer.

2. *HOXA1*: an architect gene in development and a breast oncogene

HOX genes are present among all *Bilateria* and encode transcription factors with key roles in embryogenesis. In mammals, *HOX* genes number thirty-nine, organized in four chromosomal clusters (A-D) and thirteen paralog groups (PG1-13) (Fig. 1)[27,28]. This genomic architecture parallels *HOX* gene location and expression timing during early embryogenesis in relationship with gastrulation [29]. Globally, genes residing on the 3' side of the clusters are expressed earlier and more anterior along the main body axis than genes closer to the 5' side of the clusters. This results in a temporal and spatial collinearity of expression among the clustered *HOX* genes [28,30]. The differential combined expression of *HOX* genes in the developing embryo determines the identity of body segments distributed along the body axis [29,31]. In addition to the crucial function for *HOX* genes in shaping the embryo, most *HOX* genes have also been identified to contribute to

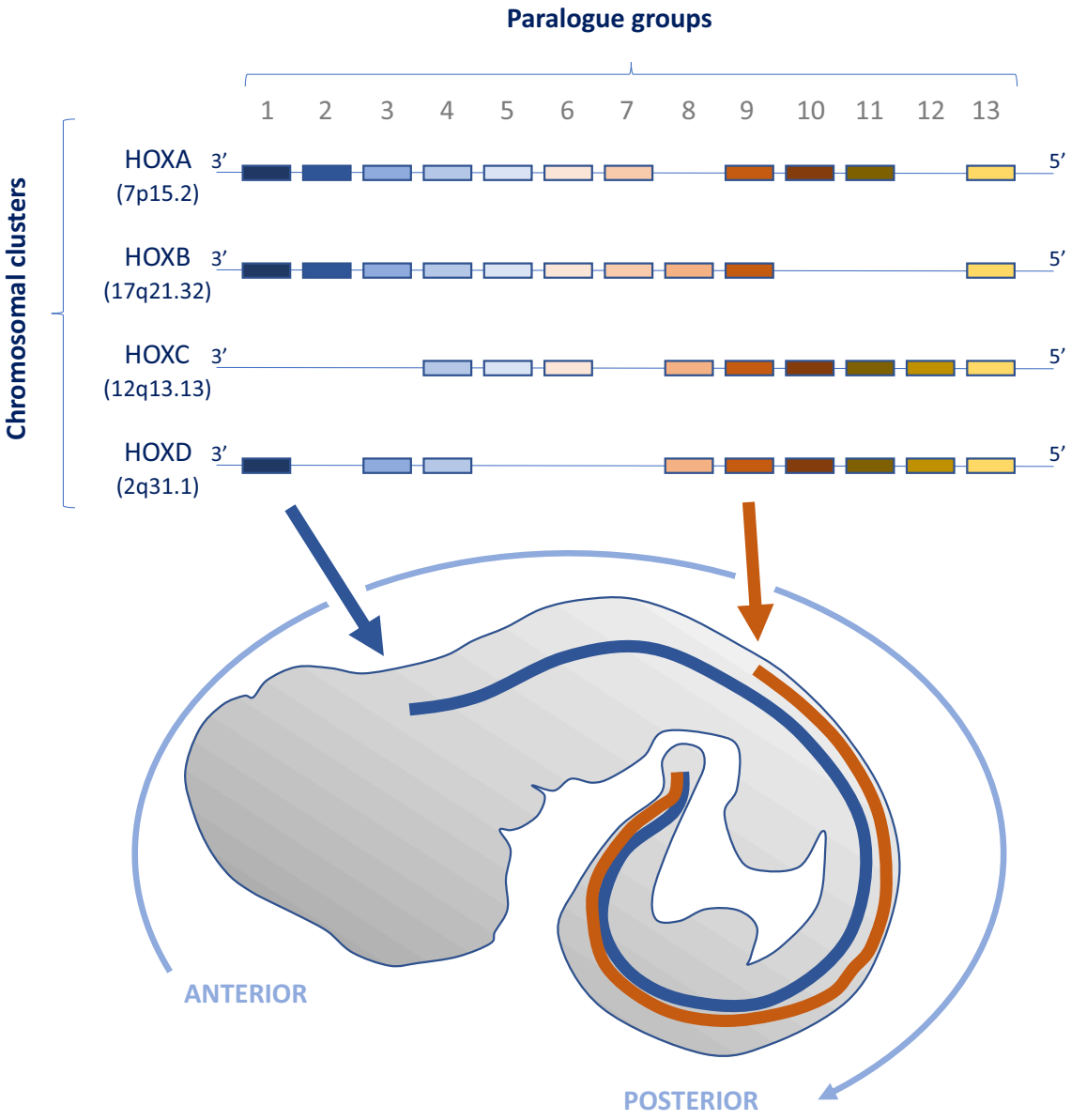

Fig. 1. The human HOX gene clusters. The human genome contains 39 HOX genes organized in 4 chromosomal clusters and defining 13 groups of paralogue genes. How gene expression follows their order in the clusters, with the genes located closer to the 3' end of the complexes being expressed earlier and showing a more anterior limit of expression than genes with a more 5' position. This leads to a collinear relationship between the location of the genes and their spatio-temporal expression profiles. This also leads to largely nested expression patterns (like depicted for HOX genes of paralogue groups 1 and 9) along the main body axis.

organogenesis. For instance, *HOXA1* is crucial for heart development [32], *HOXA3* is involved in thymus morphogenesis [33] and *HOXA5*, *HOXC6*, *HOXC8*, *HOXD8*, *HOXA9*, *HOXB9*, *HOXD9*, among others, take part in mammary gland formation [4,34–38].

HOX proteins are transcription factors that regulate downstream target genes by binding promoter DNA through their evolutionary conserved, 60-amino acid homeodomain (Fig. 2) [39–42]. Recently, genome- and transcriptome-wide analyses have documented the relationship between their functions and the genes they control [43–45]. A growing body of evidence supports additional molecular activities, in addition to their function as transcriptional regulators, for several if not all HOX proteins. These molecular roles act in the translation regulation, cell cycling, DNA repair, and signal transduction [46].

HOXA1 is one of the first *HOX* genes expressed in the gastrulating mammalian embryo. *HOXA1* plays roles in the anterior part of developing organism. It is essential to the segmentation of the hindbrain, and provides the identity to the rhombomeres, the hindbrain territories [47,48]. Indeed, *HOXA1* gene inactivation results in misshaped and misspecified rhombomeres and in impaired cranial nerve development [49]. *HOXA1* also determines the fate of neural crest cells that migrate from the hindbrain to colonize the cranio-facial territory and the arterial cardiac pole. Consequently, *HOXA1* loss-of-function also results in malformation of the heart and great arteries, and of the inner and middle ear [32,50].

Several *HOX* genes control normal mammary gland development and breast physiology [38,51,52]. In contrast, *HOXA1* is not expressed during mammary development, or during maturation at puberty or during pregnancy [53,54]. Instead, in the late 1990s, *HOXA1* expression was found in cancerous mammary cells [25,53] and *HOXA1* was later identified as a proper breast oncogene [26]. Indeed, *HOXA1* overexpression alone is sufficient to cause oncogenic transformation of mammary cells. Consistently with the oncogenic role of *HOXA1*, HOXA1 expression interference leads to a loss of cancerous cell properties [55,56]. Brock *et al.* further proved that HOXA1 expression inhibition through local injection of *HOXA1*-specific siRNA-charged nanoparticles decreased mammary tumour formation in mice [57]. Interestingly, *HOXA1* siRNA also delayed the ER expression loss typical for the most aggressive breast cancers. Finally, bioinformatic analyses unveiled HOXA1 as a key mediator of early breast cancer progression, with the significant association between high *HOXA1* expression and poor breast cancer patient outcome [58].

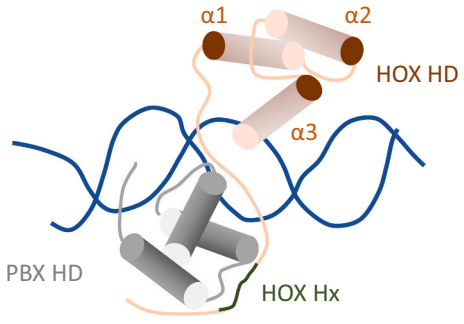

Fig. 2. DNA binding of HOX and PBX homeodomains. HOX proteins share a well-conserved 60 amino-acid long homeodomain (HD). HD adopts a helix-turn-helix conformation (HOX HD helices are represented as pink cylinders) involving one helix fitting into the major groove of the DNA (depicted as blue lines) (α3, also referred to as the recognition helix). Most HOX proteins interact with proteins of the PBC family (here PBX) which also interact with DNA with a homeodomain (in grey). The HOX-PBX interaction involves a hexapeptide (Hx, in green) residing N-terminally to the HOX HD (inspired from [40]).

3. HOXA1 inducers: triggering *HOXA1 de novo* expression in the mammary gland

Since *HOXA1* is not active in the developing or maturing mammary gland, *de novo* expression must occur in the context of breast cancer. Human growth hormone (hGH) [26], E-cadherin [59] and retinoic acid [60,61] are three identified *HOXA1* expression triggers which have been linked to breast cancer. Importantly, ERα has also been found to activate *HOXA1* expression. Probably, also other pathways likely contribute to *HOXA1* expression induction in the cancerous mammary gland (Fig. 3).

The functional connection between *HOXA1* expression and mammary cell transformation was first identified while studying the oncogenic role of mis-regulated autocrine hGH activity. *HOXA1* was found to have a pivotal role; autocrine hGH triggers *HOXA1* expression, and *HOXA1* in turn prevents apoptosis and promotes anchorage-independent cell growth [26,62]. *HOXA1* over-expression alone was sufficient for the oncogenic transformation of mammary cells, qualifying *HOXA1* as a proper oncogene [26]. hGH induces *HOXA1* expression through JAK2 activation [62,63]. Interestingly, only autocrine, but not exogenous, hGH could activate *HOXA1* and induce oncogenic cell features. Probably, autocrine hGH regulates an exclusive subset of target genes not governed by exogenous hGH [62].

Also E-cadherin (*CDH1* gene) was found to activate *HOXA1* expression, specifically via Rac1, as apparent by increased *HOXA1* expression at full confluency of the breast cancer MCF7 cell line [59]. The link between *CDH1* and *HOXA1* expression seems contradictory, since *CDH1* is considered a tumour suppressor gene, as low *CDH1* expression is a marker of poor patient prognosis in TNBC tumours [64]. In ER-positive breast cancer cell lines, estrogen can trigger ERα-mediated *CDH1* expression loss [65], critical for metastasis since it allows cell growth independently of intercellular contacts [66](Fig. 4). Therefore, the functional connection between E-cadherin and HOXA1 appears intricate and requires further investigation. In that respect, miR-100, which targets HOXA1, also targets SMARCA5, which prevents *CDH1* expression loss by promoter methylation. miR-100 expression might therefore downregulate both *CDH1* and *HOXA1*, inducing epithelial-mesenchymal transition (EMT) and hindering breast cancer development, respectively. Indeed, some EMT inducers can also inhibit tumour development [67].

Retinoic acid (RA) isomers (namely all-trans RA (ATRA), and 9-cis RA) are vitamin A derivatives that induce *HOX* gene expression in the early embryo [49,68,69]. RA activity is mediated in the nucleus by the NHR retinoic acid (RARα, β and γ) and retinoid X receptor families (RXRα, β and γ), that form RAR/RXR heterodimers and modulate gene transcription through binding to retinoic acid DNA response elements (RARE). *HOXA1* activation during hindbrain development is controlled through a 3' RARE [60,61] that is also active in breast cancer cells. Consistently, the *HOXA1* locus is bound by RARα and γ, and the *HOXA1* gene is upregulated by RA in MCF7 cancer cells [70]. ALDH1A3 activity, an enzyme that catalyses RA formation, results in *HOXA1* gene activation when its promoter is not hypermethylated. *ALDH1A3* expression correlates with poor survival and is highest in TNBC tumours. However, *ALDH1A3* expression can both induce and suppress tumour progression in mice xenografted with distinct TNBC cell lines, possibly as a result of differential *HOXA1* promoter methylation status [71].

Finally, the histone demethylase KDM3A was recently identified as a functional connection between HOXA1 and ERα [72]. KDM3A was found to regulate *HOXA1* transcription and is over-expressed in some cancers. Mahajan *et al.* next demonstrated that in the presence of Tamoxifen, ACK1, ERα and KDM3A can together activate *HOXA1* expression by binding a target sequence in its first intron. ACK1 kinase is activated by phosphorylation through receptor tyrosine kinase HER2, which in its turn is activated by heregulin. Activated ACK1 then interacts with ERα and phosphorylates KDM3A, which removes H3K9 repressive marks, triggering *HOXA1* activation (Fig. 4). ERα can thus promote *HOXA1* expression, and the authors suggested that ACK1 activation of

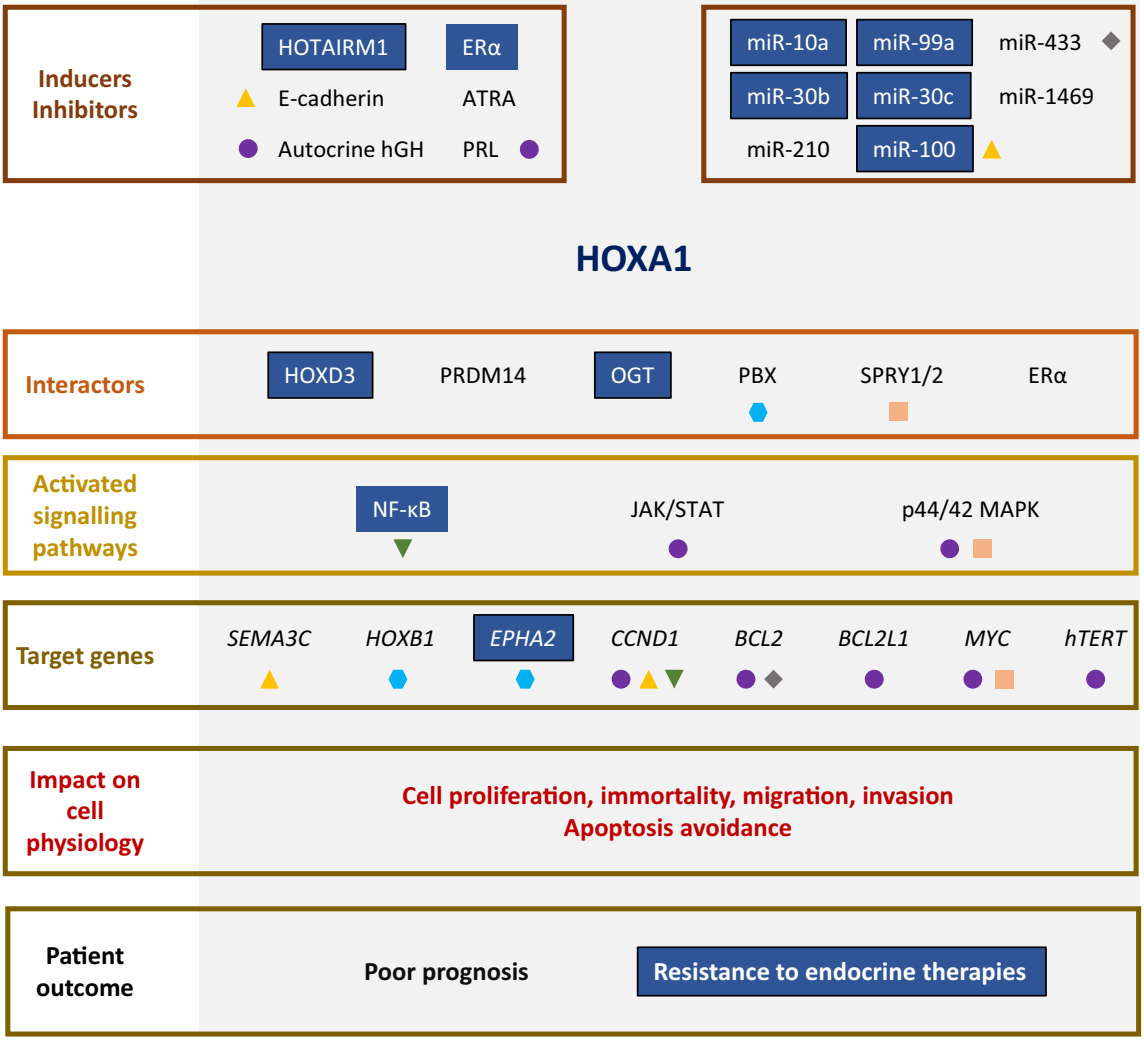

Fig. 3. Overview of HOXA1 regulations in breast cancer. Players highlighted in blue are associated with resistance to endocrine therapies. Purple rounds indicate autocrine human growth hormone (hGH) and prolactin (PRL) and their downstream players. Upwards orange triangles indicate miR-100 and its targets. Pink squares indicate SPRY1/2 and their downstream signaling and targets. Light blue hexagons indicate HOXA1 target genes identified to require PBX interaction. Downwards green triangles indicate NF-κB and its involvement in CCND1 regulation. Grey diamonds indicate mir-433 and its BCL2 regulation (see text for details).

HOXA1 expression can cause it to drive breast cancer by inducing resistance to ER modulators [73].

4. *HOXA1* expression regulation

In addition to the *HOXA1* expression regulators identified above, also regulatory RNAs and epigenetic landscape modulators control *HOXA1* expression in breast cancer or breast cancer models.

4.1. *HOXA1 and microRNAs*

Several microRNAs (miRs) have been shown to target and downregulate *HOXA1* and to change cell behaviour in the context of breast cancers. The miR-10a miRNA targets *HOXA1* mRNA and regulates its expression (Fig. 3) [74,75]. Balatti and co-workers show that miR-10a promotes breast cancer initiation and progression by downregulating *HOXA1* expression, suggesting an onco-suppressive role for *HOXA1*, but did not find differential miR-10a expression between normal breast and invasive breast cancer [74]. miR-10a activity is involved in the response of breast cancer cells to ERα modulators; it is downregulated upon relapse after Tamoxifen treatment [76]. Since miR-10a downregulation might result in *HOXA1* upregulation, this together with the ACK1-ERα-KDM3A trio presents a second connection between *HOXA1* activity and Tamoxifen resistance (Fig. 4).

The downregulation of *HOXA1* via miR-100 has been associated with inhibition of oncogenic properties in mammary tumour cells [67] as well as in cancers affecting the respiratory system [77,78]. miR-100 is downregulated in breast tumours compared to normal breast epithelium [67], and this correlates with poor prognosis [79]. Surprisingly, however, miR-100 levels appear lowest in the more benign luminal A breast cancers [67], suggesting participation of other regulatory pathways in these cancers. Finally, miR-100 can induce ERα expression in breast cancer cells, promotes luminal differentiation and sensitizes these cells to endocrine therapy [79]. Also, these results highlight the functional antagonism between HOXA1 and ERα and a putative role for HOXA1 in Tamoxifen resistance.

miR-1469 has been identified to be downregulated in breast cancer tissues [80]. Overexpression of this miR impaired the malignant behaviour of breast cancer cell lines. This oncoprotective effect was highlighted to involve HOXA1 downregulation and to be reversed by the overexpression of HOXA1. In addition, miR-1469 suppressed the activation of the PTEN/PI3K/AKT and Wnt/β-catenin pathways. This suppression could also be reverted by HOXA1, supporting a causal chain involving miR-1469 expression, HOXA1 inhibition and target pathways

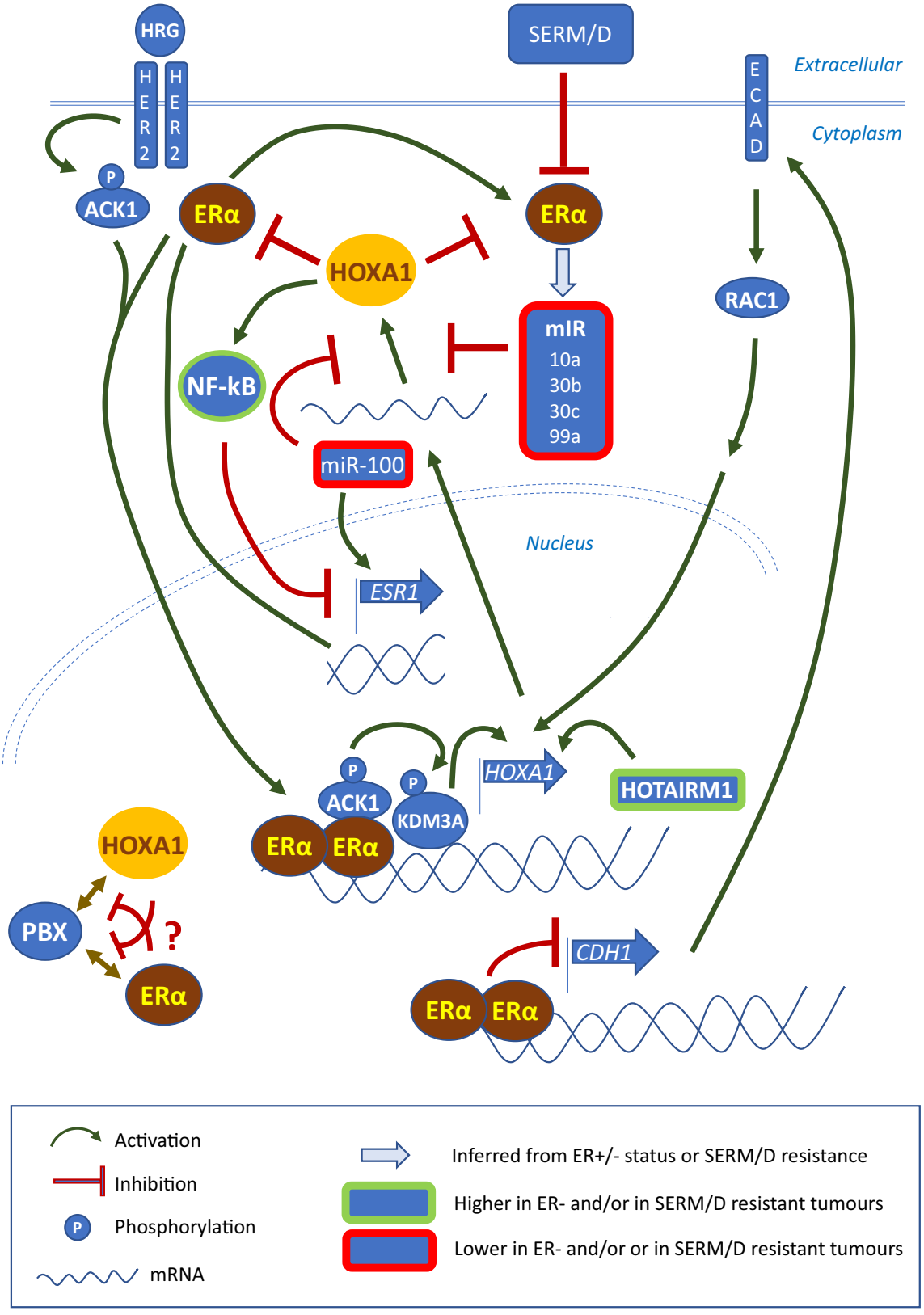

Fig. 4. Functional interactions between HOXA1, ERα and regulators (see text for details). ECAD, E-cadherin; HRG, heregulin; SERM/D selective ER selective ER modulators and downregulators.

suppression [80].

Hypoxia activates HIF-1α, a coordinator of hypoxic stress responses that involves miR-210 expression activation [81]. miR-210 can target *PTPN1, TP53I11*, and *HOXA1* under hypoxic conditions. Zhang *et al.* showed that HIF-1α-mediated upregulation of miR-210 increases cell proliferation, invasiveness and migration in the ER-positive MCF7 cell line [82]. Consistently, high miR-210 levels are associated with poor prognosis in breast cancer patients [83,84]. Indeed, miR-210 expression was found upregulated in the aggressive subtype TNBC [85], and in tumour samples from patients showing relapse following Tamoxifen treatment [76]. This role for miR-210 might result from downregulating onco-suppressors like TP53I11, which is not balanced by the down-regulation of oncogenes like *HOXA1*. The miR-210 data seem to contradict the relationship between *HOXA1* upregulation, cancer aggressiveness and endocrine therapy resistance observed with the miR-10a, miR-1469 or miR-100 regulation of *HOXA1*. This reflects the importance of more extensive correlations between transcriptomes and regulatory networks at work in specific cancer contexts.

Additional oncogenic or onco-protective miRs that can modulate breast cancer cell behaviour can target *HOXA1* in other cancer types or normal tissues. These miR-to-*HOXA1* regulatory relationships have not (yet) been highlighted but deserve to be addressed in the context of breast cancer. This holds for miR-30b and miR-30c [86–88], miR-99a [89], miR-124 [90–93], miR-142 [94,95], miR-145 [96–99], miR-150 [100–102], miR-202 [103–105], miR-433 [106–108] or miR-515 [109,110]. In addition, long non-coding RNAs (lncRNAs) and, more recently, circular RNAs (circRNAs) have been proposed to promote HOXA1 expression by "sponging" inhibitory miRs [90,94,99,109,111,112]. It remains to be confirmed whether these connections occur in breast cancer, and whether they cause oncogenic cellular changes through HOXA1 downregulation.

Quite strikingly, most of the miRs regulating *HOXA1* have been linked to ERα expression or activity and Tamoxifen resistance (Fig. 4). Therefore, combining all this information supports a functional antagonism between HOXA1 and ERα, and a role for HOXA1 in Tamoxifen resistance. Linking miR expression levels to HOXA1 and ERα expression in the different breast cancer subtypes, in relation with patient history and endocrine therapy response, is required to complete the picture.

4.2. Epigenetic changes: DNA methylation status and histone modifications in the HOXA1 locus

HOTAIRM1 (HOXA transcript antisense RNA myeloid-specific 1) is a lncRNA involved in breast cancer [113,114]. It is transcribed in antisense orientation from a region in the *HOXA* cluster between *HOXA1* and *HOXA2*. Its expression correlates to *HOXA1* expression (Fig. 3), and to basal-like breast cancer subtype [113]. *HOXA1* (and *HOXA2*) activation by HOTAIRM1 occurs through chromatin reorganization; blocking the formation of a chromatin loop and inhibiting PRC2 recruitment [115], and thereby preventing PRC2-mediated H3K27 methylation of the *HOXA1* promoter [114]. Significantly, HOTAIRM1 and *HOXA1* expression levels are higher in Tamoxifen-resistant than in Tamoxifen-sensitive MCF7 cells, and HOTAIRM1 and HOXA1 expression knock-down re-sensitizes resistant MCF7 to Tamoxifen [114](Fig. 4). Similar to how HOTAIRM1 regulates histone modifications at the *HOXA1* locus, the KDM3A histone demethylase was found over-expressed in various cancer types, where it directly activates *HOXA1* expression through histone H3K9 demethylation [72].

HOXA1 promoter methylation levels are lowest in the TNBC subtype, and significantly lower in ER-negative than in ER-positive tumours [116], again suggesting that HOXA1 and ERα activities are mutually exclusive. Consistently, the *HOXA* cluster appears more methylated in Luminal A breast tumours [117]. However, *HOXA1* has also been found hypermethylated in hereditary breast cancers, of which about one third are reported as TNBCs [118]. *HOXA1* (and *HOXA10* and *HOXB13*) hypermethylation was associated with a high proliferation index. This points out that *HOXA1* deregulation does not occur in all TNBC tumours. Consistently, *HOXA1* expression is only found in a small proportion of breast cancers (Dirk Geerts, unpublished data) and *HOXA1* deregulation effects, like for most oncogenes, appears to be context-dependent. Methylation of the *HOXA1* locus during oncogenesis does not infer the absence of HOX proteins during tumour progression since epigenetic changes are dynamic and show cell-to-cell heterogeneity, meaningful with respect to the relative proportion of cancerous cells in a tumour [9].

5. HOXA1 interactions with key players in breast cancer progression

While HOX protein expression and function has been examined for over 40 years, most molecular modes of their action remain to be identified. In particular, HOX protein interactors and cell-type specific activities remain largely uncharacterized. A notable exception are the Three Amino acid Long Extension (TALE) homeodomain transcription factors that have been extensively studied [39,119]. HOXA1 is the only mammalian HOX protein for which a proteome-wide interactome was characterized [120]. Some HOXA1 interactors are known to contribute to breast cancer biology, but their HOXA1 interaction in the context of breast cancer has not been characterized.

TALE proteins include the PREP, MEIS and PBC families. TALE proteins bind to all HOX proteins. HOX PG1-9 interact with the PBC group PBX proteins via a short hexapeptide motif (Fig. 2) [39–41]. The functional importance of the hexapeptide, and presumably the interaction with PBX, is critical for HOXA1 [121], its transcriptional activity of HOXA1 requires an intact hexapeptide [122,123]. Mice with HOXA1 hexapeptide mutations display a phenotype similar to that of *Hoxa1* null-mutant mice [123]. Consistently, HOXA1 binding sites on downstream target genes are also widely bound by TALE proteins, suggesting TALE proteins direct HOXA1 recruitment to specific binding sites [124]. The hexapeptide is essential for HOXA1 oncogenic activities in breast cells *in vitro* [55]. Indeed, a deleterious WM-to-AA amino acid substitution in the HOXA1 hexapeptide abrogates HOXA1 promotion of mammary cell proliferation, anchorage-independent cell growth, and loss of contact inhibition. These data therefore support that the HOXA1-PBX partnership is important for promoting breast cancer (Fig. 3).

Morgan and colleagues inhibited HOX-PBX interaction with short peptides mimicking the hexapeptide (referred to as HRX9), and showed that HRX9 inhibits tumour growth in many cancerous cell types [125–129]. In breast cancer, cell lines with high *HOXB1-9* expression are most sensitive to HXR9. *In vivo*, mice xenografted with the TNBC MDA-MB-231 cell line (that expresses *HOXB1-9)* and injected with HXR9 showed tumour growth retardation and longer survival [125]. This supports that the HOX-PBX interaction is crucial to the oncogenic activities of multiple HOX proteins, in a large repertoire of cancers, including solid or haematological malignancies [129]. Disruption of the HOX-PBX interaction, which has been shown to promote cell death [130,131], identifies the HOX/PBX dimers as potential therapeutic targets in combating cancers

TALE proteins were initially discovered because of their involvement in leukaemia, and are also involved in solid tumour formation independently of HOX proteins [132]. In breast cancer, PBX1 is a pioneer transcription factor for ERα (Fig. 4) [133,134]. Thus, ERα oncogenic function could also rely on its interaction with PBX. In addition, PBX1 upregulation correlates with metastatic progression and poor patient survival in ER-positive breast cancer [133,134].

A proteome-wide search for HOXA1 interactors revealed 59 candidate proteins, 41 of which were confirmed by two orthogonal assays [120]. These interactors included enzymes, cell-signalling proteins, and regulators of cell-shape and mobility, showing that HOXA1 can interact with a large variety of proteins, and supporting that HOXA1 can participate in many cell processes and changes in cell physiology in addition to its function as a transcription factor [120]. This was confirmed while studying the interaction between HOXA1, TRAF2 and

RBCK1, both modulators of the TNFα/NF-κB pathway [56]. NF-κB genes constitute a large family of transcription factors involved in cellular processes like inflammation, apoptosis and cell growth. NF-κB activation is a common process contributing to cancer development, also in breast cancer [135,136].

Aberrant NF-κB activation is frequently observed in breast cancer [120,137,138] and genetic alterations of multiple members of the NF-κB pathway are essential for cancer initiation. RBCK1 and TRAF2 have both been reported as implicated in breast cancer. RBCK1 stimulates breast cancer cell proliferation [139], TRAF2 is amplified in 15% of human epithelial cancers, including breast cancers [140]. The molecular and functional interaction between HOXA1 and RBCK1, TRAF2 and NF-κB was further validated. [56]. HOXA1 stimulates NF-κB activity independent of its transcriptional activity (see below). Most significantly, NF-κB inhibition at several levels of the pathway severely impaired the oncogenic potential of HOXA1 [56]. This, together with the inhibitory effects caused by HOXA1 hexapeptide mutagenesis, implies that both HOXA1 interaction with PBX and NF-κB activation are necessary, though not sufficient, for HOXA1-mediated oncogenesis.

Several other HOXA1 interactors were implied in breast cancer development, and might contribute to HOXA1 oncogenic activity (Table 1, Fig. 3) [141–188]. For most interactors, however, the relevance of their interaction with HOXA1 has not yet been addressed in breast cancer, meriting further investigation. One example is PRDM14, a putative histone methyl-transferase involved in primordial germ cell fate, that is hardly expressed in adulthood [189,190]. PRDM14 shows over-expression in breast cancer, especially in metastatic tumours [66]. PRDM14 promotes cell growth, and its knockdown decreases stemness, tumorigenicity and metastasis [189,191]. However, PRDM14 reduces HOXA1 half-life and activity [192], and in other cancer types than breast cancers, DNA methylation at the *PRDM14* gene promoter has been observed [193]. PRDM14 would therefore display either oncogenic or tumour suppressor activities depending on the cellular context. Understanding the PRDM14-HOXA1 relationship in breast cancer will clarify the interplay between HOXA1, NF-κB and ERα. Indeed, NF-κB pathway genes are up-regulated and *ESR1* (ERα gene) promoter methylation is

Table 1
Genes encoding proteins which interact with HOXA1 and their relations with cancer (C) or breast cancer (BC).

Interactor name		References
ADAMTSL4	C	[141-143]
EFEMP2	BC	[144, 145]
FHL5	C	[146]
HOXD3	BC	[147, 148]
IKZF2	BC	[149]
KRT81	BC	[150, 151]
LIMS1/PINCH1	BC	[152]
LNX2	C	[153, 154]
LPXN	BC	[155]
MDFI	BC	[156]
MGAT5B	BC	[157, 158]
OGT	BC	See text for details
PDCD6IP/ALIX	BC	[159]
PDLIM7	C	[160, 161]
PFKM	BC	[162]
PITX2	BC	[163]
PLSCR1	BC	[164, 165]
PRDM14	BC	See text for details
RAB33A	BC	[166]
RBCK1	BC	See text for details
RBPMS	BC	[167, 168]
RGS20	BC	[169, 170]
SMOC1	C	[171-174]
SPRY1	BC	[117, 175-178]
SPRY2	BC	[175, 179]
TRAF1	BC	[180, 181]
TRAF2	BC	See text for details
TRIM23	C	[182-184]
TRIP6	BC	[185, 186]
ZBTB16	BC	[187]
ZBTB32	BC	[188]

A black box indicates that the interactor has been identified as stimulating cancer initiation or progression and accordingly relates to poor prognosis. A grey box indicates that both oncogenic and oncosuppressive activities have been associated to the interactor. HOXA1 interactors for which no relationship with cancer has been reported so far were not included in the table.

enhanced upon PRDM14 over-expression [191].

Another example is OGT, a unique cytoplasmic and nuclear O-linked-β-N-acetylglucosamine (O-GlcNAc) transferase, that transfers GlcNAc from UDP-GlcNAc onto serine and threonine residues of target proteins, including HOXA1 [194,195]. Since UDP-GlcNAc is the final product of the hexosamine pathway, its abundance depends on glucose uptake. OGT and O-GlcNAc levels both increase in breast cancer cells, what could be explained by their increased metabolism [196,197]. OGT inhibition decreases tumour growth [196], and induces cell cycle arrest and apoptosis. This effect is stronger in TNBC cell lines than in ER/PR-positive cell lines, indicating that TNBC cell lines are more dependent on OGT expression [198]. O-GlcNAcylation stimulation in MCF7 cells leads to decreased ERα expression, and resistance to Tamoxifen [199]. The molecular roles of OGT and HOXA1 O-GlcNAcylation in HOXA1 breast cancer oncogenicity remains to be analysed.

6. HOXA1 downstream: target genes and pathway modulation in breast cancer

6.1. Target genes

Many studies reported on HOXA1 downstream target genes, but only few data exist on HOXA1 function as a transcriptional regulator in the context of breast cancer [26,59,63,200,201]. Studies on HOXA1 target genes or target loci on the chromatin in the mouse embryo or in cell models of early development have highlighted downstream target genes which might also be relevant to HOXA1's role in breast cancer [50,202] (Fig. 3).

As described above, *HOXA1* can be activated by autocrine hGH in breast cancer cells. hGH signalling activates STAT3/5B and p44/42 MAPK signal transduction pathways that control known HOXA1 target genes like *BCL2*, *BCL2L1*, and *CCND1* [26,58,63,200]. HOXA1 and hGH signalling converge on shared target genes, as was confirmed by *HOXA1* knockdown resulting in decreased transcriptional activation of *BCL2, CCND1* and *MYC* by autocrine hGH [62]. HOXA1 also induces expression of the prolactin receptor (PRLR). Activation of the prolactin pathway can also mediate HOXA1 oncogenic effects, through the STAT5A/B and MAPK pathways [201]. This is consistent since while hGH receptor is activated by hGH, PRLR can be activated by both GH and prolactin (PRL) [203].

Activation of the p44/42 MAP kinase pathway is a very frequent event in tumorigenesis [204,205]. The expression levels of GRB2, MEK1, SDFR1, IER3, EPAS1, PCNA and CAT, all part or downstream of the p44/42 MAP kinase pathway, were higher in MCF7 cells with, than in MCF7 cells without HOXA1 expression [200]. Consistently, upon siRNA-mediated HOXA1 knockdown in MCF7 cells, expression of each of these genes was decreased, a result recently confirmed *in vivo;* injection of *HOXA1*-targeting siRNA reduces mammary tumour cell proliferation through downregulating p44/42 MAPK signalling [57].

STAT3 and -5 play important roles in embryogenesis and mammary gland organogenesis by regulating cell cycle progression and apoptosis [206,207]. In breast cancer however, they can be constitutively activated, decreasing apoptosis and increasing cell proliferation and anchorage-independent growth [63,208–211]. Mohankumar *et al.* showed that HOXA1 over-expression in immortalized human mammary epithelial cells upregulated STAT3 and STAT5A/B mRNA and protein levels and phosphorylation of STAT3 and STAT5B, but not of STAT5A. This HOXA1-mediated STAT3/5 activation is sufficient to transform immortalized human mammary epithelial cells [63]. STAT3 DNA binding can also be enhanced by an HOXA1 interactor called granulin (GRN), whose expression correlates with poor patient prognosis [212]. A final link between HOXA1 and STAT3/5 signalling is MYC. MYC can be activated by STAT3/5 signalling [211], and mediates the oncogenic effects of HOXA1 stimulation by hGH [62].

Cell division stimulation, apoptosis inhibition, replicative immortality, and cell migration and invasiveness are all important hallmarks of cancer [213]. As a transcription factor, HOXA1 regulates target genes that are key contributors to several of these hallmarks. *CCND1*, or cyclin D1, controls G1 to S cell cycle phase transition with its partner kinases CDK4 and CDK6. Its over-expression in breast cancer was linked to metastasis and poor prognosis, suggesting a role in cell migration [214]. *CCND1* is downregulated upon HOXA1 inhibition [58,214]. HOXA1 can also promote *BCL2* expression [26,215]. BCL2 family members BCL2 and BCL-X_L counteract apoptosis by interacting with pro-apoptotic BCL2 family proteins like BAX [216–218]. HOXA1 inhibition in breast cancer leads to decreased BCL2, but increased BAX levels and, therefore, increased apoptosis [58]. Telomere maintenance and replicative immortality are allowed by hTERT. hTERT is also involved in other oncogenic cell features like cell migration and invasion [219]. HOXA1 can enhance *hTERT* transcription [26]. SEMA3C also promotes breast cancer cell migration [220–222]. HOXA1 can upregulate SEMA3C during embryo development [50]. Consistently, miR-100 over-expression, and thereby *HOXA1* downregulation, correlates with decreased expression of HOXA1 target genes like *SEMA3C* and *CCND1* [67].

Finally, two well-characterized hindbrain development HOXA1 target genes might also be relevant to its oncogenic activity. *HOXB1 is* a direct target of HOXA1 and PBX during hindbrain segmentation and rhombomere 4 identity establishment [49,50]. It is over-expressed in some breast tumours, and HOXB1-PBX interaction blocking using the peptide HRX9 decreased tumour growth [125]. The *EPHA2* ephrin receptor gene is regulated by HOXA1 and PBX1 in establishing rhombomere boundaries during hindbrain segmentation [223], and a recognized inducer of cell proliferation during mammary gland development [224]. *EPHA2* over-expression is sufficient to induce oncogenic transformation of mammary epithelial cells, just like *HOXA1* [26,225]. *EPHA2* expression is correlated to breast cancer subtypes [226]. For example, low expression of *EPHA2*-targeting miR-200a fosters TNBC cell migration, and *EPHA2* over-expression correlates with poor prognosis in TNBC patients [227]. *EPHA2* expression is inhibited by estrogen and is associated with Tamoxifen resistance in ER-positive cells transplanted in mice [228] (Fig. 3). Zelinski and co-authors suggest that ERα loss in TNBC promotes cancer aggressiveness by releasing this *EPHA2* inhibition [229].

6.2. HOXA1 as a signalling modulator: NF-κB activation

As mentioned above, blocking HOXA1-mediated NF-κB pathway activation inhibits HOXA1 tumorigenicity, confirming the importance of NF-κB in HOXA1 oncogenic function [56]. NF-κB constitutive activation is correlated to a basal-like breast cancer subtype [230], endocrine therapy resistance, and poor patient prognosis [215,231,232](Fig. 4). Interestingly, we found the strongest correlation with *HOXA1* expression for this subtype (Dirk Geerts, unpublished data).

NF-κB and *HOXA1* transcription factors act as breast oncogenes. Prompted to interrogate breast cancer transcriptome databases, we found very strong correlations between *HOXA1* and NF-κB signalling network genes [56]. In addition, HOXA1 protein physically interacts with modulator proteins of the NF-κB pathway; HOXA1 activates the NF-κB pathway at the protein level, not as a transcription factor. Indeed, HOXA1 expression resulted in the activation of upstream regulators of NF-κB and the stimulation of NF-κB nuclear entry. Blocking the NF-κB pathway at the level of the IκB inhibitor or at the level of TRAF2, both in the cytoplasmic part of the signalling network, inhibited HOXA1 action [56]. A TRAF2 dominant-negative mutant was epistatic towards HOXA1 impact on NF-κB signalling. Finally, mutant HOXA1 proteins that cannot bind DNA or interact with PBX, and that have no transcriptional function, remain active in simulating NF-κB. Thus, HOXA1 would act as a proper pathway regulator at early signalling steps, upstream or at the level of the TRAF2 and RBCK1 modulators.

6.3. A functional antagonism between HOXA1 and ERα?

Above, we presented evidence for HOXA1-ERα crosstalk (see also Fig. 4). Mahajan *et al.* showed that, together with ACK1 and KDM3A, ERα can activate *HOXA1* expression, promoting breast cancer cell growth and Tamoxifen resistance [73]. Numerous miRs that modulate HOXA1 expression are also involved in ERα regulation and Tamoxifen resistance. miR-30c expression correlates with ERα levels and predicts benefit from endocrine therapy, miR-100 can induce ERα expression, and miR-10a is involved in Tamoxifen resistance [8,76,79,88,233]. Injection of *HOXA1*-targeting siRNAs in mice prevents the loss of *ESR1* expression [57]. These distinct connections between HOXA1 and ERα strongly suggest a functional antagonism between these proteins. Consistently, based on bioinformatic analysis of breast cancer transcriptomes, we recently unveiled an extremely strong and opposite correlation between the *HOXA1*-ER expression in breast cancers and mRNA expression of 2486 genes [234]. Among these genes, about half are positively correlated with *HOXA1* and negatively correlated with *ESR1*, with the other half showing the opposite. We also demonstrated that HOXA1 can inhibit ERα activity *in vitro*. Interestingly, this inhibition requires an intact, DNA-binding, HOXA1 homeodomain, but also involves its ability to activate NF-κB which is DNA binding-independent. HOXA1 action on ERα signalling would therefore be at least bimodal [234]. Similarly, NF-κB can repress ERα expression via at least three distinct mechanisms involving the PRDM1 zinc finger protein, the PKCθ serine/threonine kinase, and the EZH2 methyltransferase [231,235–237]. Oida *et al.* also showed that Tamoxifen-resistant MCF7 cells have lower ERα expression because of NF-κB activity, since this ERα downregulation can be rescued by inhibiting the NF-κB upstream regulator IKKβ. The authors further identified that NF-κB is not only able to inhibit ERα gene expression but can also interfere with ERα protein activity [238]. Therefore, subsequently to HOXA1 activity, cell growth control could switch at least in part by NF-κB inhibiting ERα and decreasing cell sensitivity to endocrine therapy.

In the context of this complex HOXA1-ERα interplay, it is worth noticing that both proteins share the ability to control key regulators of cancer. *BCL2* and *CCND1* are common HOXA1/ERα downstream target genes, and effectors of their oncogenic activities. Like HOXA1, ERα also promotes cell proliferation through Cyclin D1 regulation [239,240]. Similarly, both HOXA1 and ERα can cause apoptosis evasion through *BCL2* regulation. ERα can activate *BCL2* expression by a direct binding on a cis-regulatory element in its coding sequence [241]. Thus, if during cancer development, a switch occurs from ERα-positive to HOXA1-positive, as it has been proposed in the acquisition of endocrine-therapy resistance (see above, [73]), cell cycle progression through *CCND1* and apoptosis inhibition through BCL2 control would remain intact. Whether other hallmarks of cancer are similarly controlled by ERα and HOXA1 or are sustained by alternative, compensating, pathways is an important issue to be addressed. It could lead to an understanding of changes in cancer development that make it amenable for adaptative therapeutic strategies.

7. Other *HOX* genes in breast cancer

HOX proteins do not share extensive similarities, in particular between different paralog groups. A notable exception is their very well-conserved homeodomain, that is responsible for the binding to promoter DNA of their downstream target genes, as well as probably for additional interactions. *HOX* expression dysregulation shows how embryogenesis and neoplasia are connected processes. *HOX* genes are all expressed in embryo development and deregulation of their expression has been identified in many types of cancer [21]. Abate-Shen summarized it merely: "[…] most cases of deregulated homeobox gene expression in cancer conform to a simple rule: those that are normally expressed in undifferentiated cells are upregulated in cancer, whereas those that are normally expressed in differentiated tissues are downregulated in cancer." [242,243]. The connection between the known functions of HOXA1 and its oncogenic potential however is not straightforward. The main functions identified for HOXA1 during embryogenesis consist in patterning embryonic territories (hindbrain, neural crest cells, somites). At the cellular level, however, to what extent HOXA1 modulates cell division, apoptosis or migration during developmental processes remains elusive. Recent data from RA-induced differentiation of embryonic stem-cells identified cross-regulatory relationships and shared target genes between NANOG and HOXA1, supporting an interplay in the balance between cell stemness and differentiation fates [244]. This is relevant to the neuro-ectodermic differentiation. Thus, all together, the mechanistic connection between HOXA1 action mode during embryo development and the HOXA1 influence on mammary cell biology remains unknown. The only known connection relies on target genes (e.g. EphA2, see above) and interactors (e.g. PBX, see above) that are clearly involved in the developmental activities of HOXA1 as well as in breast cancer biology.

Unlike HOXA1, which is not expressed during breast development, other HOX proteins, mainly from the PG 9 to 13, control mammary gland development [4,34–37,54,245,246]. Thirty-five of 39 *HOX* genes as well as the long non-coding RNA HOTAIR have been associated to breast cancer development, but only a handful have properly been shown to be involved in tumour initiation, progression or, on the opposite, suppression (for details, see [21,54]). In addition to HOXA1, three HOX proteins have been more deeply studied in the context of breast cancer; HOXA5, which acts as a tumour suppressor (see below), and the oncoproteins HOXB7 and HOXB13 (see below). Strikingly, the different HOX proteins in breast cancer do not act through similar molecular mechanisms.

HOXA5 is mainly expressed in mammary duct epithelium, where it controls normal cell proliferation and differentiation [34,247]. *HOXA5* expression is decreased in breast cancer [247], and then no longer upregulates *PR* gene and the *TP53* tumour suppressor gene. While the consequences of PR activation have not been identified, HOXA5 activation of *TP53* can promote apoptosis [248,249], probably in part by its interaction with the anti-apoptotic basic helix-loop-helix protein Twist, when it prevents Twist-mediated inhibition of *TP53* target genes [250]. Independently of *TP53*, HOXA5 can promote apoptosis through caspases 2 and 8 [251]. Finally, HOXA5 was also found to inhibit angiogenesis [252]. Taken together, these data support that, oppositely to HOXA1, HOXA5 acts as a tumour suppressor in breast cancer.

In contrast, *HOXB7* is over-expressed in breast cancer, especially in metastatic tumours [253–256]. HOXB7 over-expression promotes cell proliferation, EMT, invasion and angiogenesis and inhibits apoptosis [254,255,257]. It has been suggested that, like for HOXA1, HOXB7 action depends on the presence of its TALE cofactors to promote oncogenesis [55,258]. However, Jin and colleagues showed that HOXB7 acts as ERα co-activator at ER-binding sites in its target gene promoters. The complex formed by HOXB7, ERα and additional cofactors can e.g. promote *HER2* transcription, which causes poor patient prognosis in ER-positive cancers. The functional relationship between HOXB7 and ERα appears synergistic, opposite to HOXA1 inhibition of ERα activity. Strikingly, *HOXB7* over-expression can also trigger Tamoxifen resistance, but through EGFR signalling [259].

HOXB13 promotes cell invasion and is indeed over-expressed in breast cancer metastasis [260]. *HOXB13* expression is positively correlated to *IL6* expression, and negatively correlated to *ESR1* expression status, and thereby linked to Tamoxifen resistance and poor patient prognosis. HOXB13 inhibits ERα expression by directly binding a TAAT sequence in the *ESR1* promoter [260], suggesting ER inhibition at the level of gene regulation rather than at the level of the ERα protein activity.

8. To conclude about HOXA1 in breast cancer: a big picture with question marks…

Although HOXA1 dysregulation occurs in a relatively low proportion of breast cancers, with the wide occurrence of mammary neoplasia among women, *HOXA1* activity still concerns an important absolute number of patients. Consequently, it is worth investigating the oncogenic activity of HOXA1, and to establish the causal relationship between *HOXA1* upregulation and breast cancer subtype and patient survival. In fact, *HOXA1* activity is highest in TNBCs, the most aggressive breast cancer subtype.

From a mechanistic point of view (as summarized in Fig. 3), a wealth of information has been reported identifying multiple regulatory pathways for de novo HOXA1 induction in breast tissue, which also includes the relief of inhibitions mediated by mIRs. Some connections remain hypothetical: have only been highlighted in cell models, or in the context of other cancers than breast cancers. Next, experimental data as well as bioinformatic analyses of clinical samples strongly support that HOXA1 oncogenic activity requires interaction with PBX and NF-κB pathway activation. Several lines of evidence suggest that HOXA1 antagonizes ERα activity (Fig. 4), and thereby contributes to endocrine therapy resistance, a major clinical problem in treating breast cancer. In addition, numerous HOXA1 interactors are known to be involved in breast cancer initiation or progression, although the actual connection with HOXA1 in breast cancer still awaits further investigation (Table 1). Finally, HOXA1 target genes identified in cancer cell models or developmental models (e.g. stem cells) appear to be key regulators cancer hallmarks [213]: cell division stimulation, apoptosis inhibition, cell immortalization, migratory and invasive behaviours, etc. Finally, bioinformatic analysis of genome- and transcriptome-wide breast cancer databases show correlations between *HOXA1* expression and breast cancer signalling pathways or cellular processes, however, whether these correlations underpin causal relationships also needs further investigation.

Although data on the molecular role of *HOX* genes in breast cancer remain fragmentary, all evidence point at specific roles for the different *HOX* genes, either tumorigenic or tumour-suppressive, with unique rather than shared molecular activities for each HOX family member. Defining the specific molecular mechanisms that provide HOXA1 and HOX proteins with their oncogenicity is crucial for a better understanding of cancer aetiology and for the development of new therapeutic strategies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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