ALDH1A1 in breast cancer: A prospective target to overcome therapy resistance (Review)

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Abstract. The expression of cytosolic aldehyde dehydrogenases (ALDHs), which mediate the last step in the pathway of the synthesis of all-trans retinoic acid, is dysregulated in various types of human cancer, and has been associated with the development of cancer stem cells (CSCs) in solid tumors and hematological malignancies. CSCs are considered a minor fraction of cancer cells with the capacity to initiate neoplastic tumors. ALDH1A1 serves a crucial role in the emergence of the CSC phenotype, induces the malignant behavior of cancer cells and promotes treatment resistance. Notably, ALDH1A1-induced therapy resistance is not exclusive to just one group of drugs, but affects diverse types of drugs that use different mechanisms to kill cells. This diversity of drug resistance-inducing effects is associated with the stemness-supporting functions of ALDH1A1. The inhibition of ALDH1A1 activity using chemicals or the depletion of ALDH1A1 via genetic approaches, such as the use of small interfering RNA, can overcome diverse pathways of therapy resistance. In the context of breast cancer, it is critical that only a fraction of malignant cells are expected to manifest stem-like features, which include increased expression of ALDH1A1. From the angle of disease prognosis, the extent of the association of ALDH1A1 with increased malignant behavior and drug resistance remains to be determined through the application of cutting-edge methods that detect the expression of tracked biomarkers within tumors.

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Contents

1. Introduction

The expression of cytosolic aldehyde dehydrogenases (ALDHs), which mediate the last step in the synthesis of all-trans retinoic acid (ATRA), is dysregulated in various types of human cancer, and is associated with the development of cancer stem cells (CSCs) in both solid tumors and hematological malignancies (1,2). CSCs are considered a minor fraction of cancer cells with the capacity to initiate neoplastic tumors. The purification of CSCs from patient samples, in almost all cases, requires antibodies against specific surface markers or the use of specific culture conditions to promote the enrichment of CSC populations. Therefore, these methods require identification of CSC-specific markers that are not available or adequate in a number of types of cancer (3). The expression of retinaldehyde dehydrogenases, of which ALDH1A1 is one, has been included in the biomarkers that are most often used for breast CSCs (4-6) together with the hyaluronic acid receptor CD44 (7) and glycoprotein CD133 (8,9). While ALDH1A1 does not have a uniform impact on cancer cells, it does nevertheless acquire a crucial role under certain conditions, which is associated with resistance to certain aspects of oxidative stress and the generation of RA, as discussed in the present review. The elucidation of the precise mode of regulation of this enzyme and of the gene that encodes it are therefore of paramount importance in biology.

2. ALDHs: General information

ALDHs are evolutionary well-conserved enzymes in all living taxonomic groups from bacteria to mammals (10). Previous

studies have demonstrated that ALDH enzymes are involved in various biological processes, such as proliferation, differentiation and immune system regulation, by participating in the detoxification of aldehydes (10-12). Notably, ALDH proteins may function in the process of cellular UV absorption, and have also been shown to bind various compounds, such as endobiotics, xenobiotics, androgens and thyroid hormones (11,12). Although ALDH activity and expression are generally high in mitochondria-rich organs, such as the liver and kidney, their expression is not specific to these organs and ALDH enzymes have a wider expression profile throughout the body (13).

ALDH family enzymes catalyze the oxidation and thereby the detoxification of aldehydes, which are highly toxic and reactive molecules generated from various endogenous or exogenous sources (14,15). The generation and accumulation of endogenous aldehydes depends on cellular activities that take place during various metabolic processes, such as amino acid/alcohol metabolism and lipid peroxidation in cells (16). Aldehydes are also abundantly present in the environment and in may be taken up from water, food and air (17).

Although the substrates of ALDH family members are generally called 'aldehydes', these substrates are diverse aldehyde molecules that differ according to the substrate-binding characteristics of the different ALDH subtypes; these binding characteristics depend on the amino acid sequences and structural properties of each ALDH protein. Further adding to the subtype diversity, ALDH family proteins can be localized in different cellular compartments, such as the cell membrane, cytoplasm, nucleus, endoplasmic reticulum, mitochondria and in lipid droplets (18). In humans there are 19 ALDH proteins, and these proteins can be divided into 11 different classes, as follows: Class I (ALDH1A1, ALDH1A2, ALDH1A3, ALDH1B1, ALDH1L1 and ALDH1L2), Class II (ALDH2), Class III (ALDH3A1, ALDH3A2, ALDH3B1 and ALDH3B2), Class IV (ALDH4A1), Class V (ALDH5A1), Class VI (ALDH6A1), Class VII (ALDH7A1), Class VIII (ALDH8A1), Class IX (ALDH9A1), Class X (ALDH16A1) and Class XI (ALDH18A1) based on their amino acid sequence similarities (19). Recently Xanthis *et al* (10), suggested that the mitochondrial enzyme ALDH2, which accounts for most acetaldehyde detoxification, should be included in Class I due to its high amino acid sequence similarity to the Class I ALDH proteins; notably, there are important differences between members of this broad class (Class I) regarding the substrate binding pocket and in the rate-limiting step (20). The Class I subclass composed of ALDH1A1, ALDH1A2 and ALDH1A3 has a unique role; these proteins function as retinaldehyde dehydrogenases, and are the main enzymes required for the biosynthesis of RA in the cytosol (21), having a larger substrate binding cleft that allows them to work more efficiently on large aldehydes (22,23).

In healthy cells and tissues, the controlled expression and activities of ALDH family proteins contribute to the maintenance of homeostasis. In this context, the scavenging of aldehydes via the activities of ALDH proteins is an important process in preventing oxidative stress caused by aldehydes in cells (24). However, the current approach to cancer treatment is generally based on inducing oxidative stress in tumor cells via chemotherapy or radiotherapy, causing substantial cell damage and consequently promoting cell death (25). Therefore, an increase in the expression or activity of ALDH family proteins may negatively affect the success of therapy (26). Notably, it has long been considered that ALDH family proteins may participate in cancer-related processes (27,28). Several members of this family, including ALDH1A1, have been extensively studied for their contributions to the emergence of the CSC phenotype in malignant cells (29).

3. ALDH1A1

ALDH1A1 has a mostly cytoplasmic and lesser nuclear localization in cells, and commonly uses aliphatic aldehydes as substrates, including 4-hydroxynonenal (4-HNE), malondialdehyde (MDA) and retinaldehyde, which are lipid peroxidation products, among a number of different compounds (16,30,31).

ALDH1A1 expression and activity are regulated by various mechanisms. For example, prostate tumor overexpressed 1 (PTOV1) directly binds to the ALDH1A1 promoter and increases its expression (32). Notably, it is well known that PTOV1 levels are increased in the tumors of some patients with breast cancer (BCa), and that PTOV1 upregulation is associated with disease progression and poor prognosis (33). Although, to the best of our knowledge, no functional studies have been conducted on this subject, the tumor-promoting effect of PTOV1 may be related to the increased expression of ALDH1A1, at least in part.

Mucin 1 (MUC1) expression is increased in various types of cancer, including BCa, and elevated MUC1 expression can promote the malignant behavior of cancer cells (34,35). Furthermore, MUC1 is involved in chemotherapy resistance in cancer (36). It has been shown that MUC1 induces ALDH1A1 expression via activation of ERK and then phosphorylation-coupled activation of C/EBPβ. Activated C/EBPβ directly binds to the ALDH1A1 promoter and increases its expression (37). Notably, it has been reported that MUC1 silencing inhibits the CSC phenotypic manifestation of BCa cells (38). ALDH1A1 expression may also be regulated in a Wnt/β-catenin-dependent manner in BCa (39); the β-catenin/TCF complex directly binds to the ALDH1A1 promoter and increases its expression (40). In addition, β-catenin depletion has been shown to decrease ALDH1A1 expression (41).

Although not yet demonstrated in BCa, to the best of our knowledge, Smad4 has been shown to bind to the ALDH1A1 promoter and suppress its transcription in TGF-β-treated pancreatic cancer cells (42). Although TGF-β inhibits tumorigenesis in normal healthy cells and early-stage cancer, it mainly promotes invasion, metastasis and therapy resistance by promoting epithelial-mesenchymal transition (EMT) in advanced-stage cancer (43-46). In this sense, it will be important to reveal the effects of the decrease in ALDH1A1 expression that is mediated by TGF-β/Smad4, by using detailed mechanistic approaches in terms of identifying and characterizing downstream targets and analyzing their impacts on cancer biology in diverse model systems, such as organoids.

NFκB has also been shown to bind directly to the ALDH1A1 promoter and to positively regulate its expression (47), although this has not yet been demonstrated in BCa. NFκB is a well-known pro-inflammatory transcription factor that is involved in the pathogenesis of BCa and other types of cancer

by controlling the expression of various genes involved in proliferation, invasion, metastasis and drug resistance (48-50). However, it is known that NFκB has a tumor-suppressing role in addition to its tumorigenesis-promoting role (51); in this sense, the physiological consequences of NFκB-induced ALDH1A1 expression need to be studied further in terms of cancer biology. Post-translational mechanisms are also important in the regulation of ALDH1A1 activity. It has been shown that acetylation of the K353 amino acid residue is important for ALDH1A1 activity in BCa cells (52); acetylation of this residue by P300/CBP-associated factor results in inhibition of ALDH1A1 activity, whereas its de-acetylation by SIRT2 results in ALDH1A1 activation (52). Phosphorylation of ALDH1A1 by Aurora kinase A on the T267, T442 and T493 amino acid residues increases both its intracellular stability and activity; these effects can be attributed to a decrease in ALDH1A1 ubiquitylation, and an increase in the conversion of ALDH1A1 from an oligomeric to a monomeric form (53). Although this study was conducted in pancreatic cancer cells, its findings may also apply to other types of mammalian cells.

ALDH1A1 uses retinaldehyde as a substrate. Retinaldehyde is an intermediate product in vitamin A metabolism. Vitamin A is a lipid-soluble molecule that cannot be synthesized in mammals and therefore needs to be taken up from food (54,55); however, it has critical roles in normal cellular physiology and its deficiency may result in various pathological conditions, including inflammation. Vitamin A exists in three forms within cells: Retinol, retinaldehyde and RA. RA is the most active form and its generation from retinol occurs through two basic enzymatic reactions. In the first step, retinol is converted to retinaldehyde by the oxidation activities of alcohol dehydrogenases and in the second step, retinaldehyde is oxidized to RA by the activities of ALDH family members (56). Retinaldehyde formation by oxidation of retinol is a reversible process, as retinaldehyde can be reduced back to retinol by retinal reductases (57). However, the generation of RA by oxidation of retinaldehyde is an irreversible process and RA is rapidly degraded by P450 family enzymes after it is generated (56).

RA signaling generally works in an autocrine and paracrine manner, and after RA is produced it binds to RA receptor (RAR) and retinoid X receptor (RXR), which are members of the nuclear receptor family (58). Consequently, in the nucleus, ligand-activated receptors (RARα, β and γ, which form RA-induced heterodimers with RXRα, β and γ) bind to RA response elements on the promoters of RA responsive genes and regulate their expression (59). Generated RA is thereby involved in various cellular processes, such as development and differentiation. ATRA, 9-cis RA and 13-cis RA are natural RA isomers, and their receptor preferences may differ from each other in RA signaling (60). In this context, although ATRA selectively binds to RAR, 9-cis RA can bind to both receptor types (RAR and RXR) (61). Although activated RAR and RXR regulate the expression of target genes by establishing homo- or hetero-complexes in the canonical pathway, it is known that these receptors (especially RXR) can affect cell physiology by forming hetero-complexes with other receptors, such as estrogen receptor (ER) or peroxisome proliferator-activated receptor (PPAR) (62-64). PPAR alone can be activated by RA; however, in contrast to RAR, PPAR signaling supports cell survival and proliferation, but PPAR requires a higher concentration of RA to be activated when compared with RAR (63). This multiplicity of downstream effectors allows RA to affect a number of signaling pathways, including PI3K/AKT, Notch and Wnt/β-catenin, and to consequently regulate several cellular functions (65). The effects of RA on cells therefore depend on the proteome of the cell, and also on the type and concentration of RA, which determine the subsets of receptors that will be activated.

ALDH1A1 also uses 4-HNE and MDA as substrates. Regarding the most common aldehydes that are products of lipid peroxidation, 4-HNE induces chemical modifications on DNA, and thereby causes DNA damage and mutations (66). Notably, it has been shown that 4-HNE forms an adduct at codon 249 of the p53 encoding gene in the human genome and promotes liver cancer malignancy (67). In addition, 4-HNE can modify proteins directly. In the context of DNA damage, it has been shown that 4-HNE reduces the activities of DNA damage repair proteins, resulting in more severe damage to DNA, under oxidative stress conditions (68). Notably, increased 4-HNE levels are involved in carcinogenesis, and excess accumulation of 4-HNE has been reported in various types of cancer, including esophageal, colon and lung cancer (69-71).

Another reactive aldehyde, MDA, is an end product in the peroxidation of polyunsaturated fatty acids found in the cell and mitochondrial membranes, and has long been used to monitor lipid peroxidation (16,72). An increase in MDA levels may reflect a decrease or insufficient activity of antioxidant systems, and this event has been associated with various neoplastic (including BCa) and non-neoplastic diseases (73-75). MDA activity is pH-dependent and MDA strongly reacts with basic amino acids, such as lysine and arginine, at lower pH values, to generate adducts with free amino acids or proteins (16,76). MDA also reacts with aminophospholipids and generates adducts such as MDA-phosphatidylethanolamine (77). In addition, MDA reacts with DNA to generate adducts, and consequently induces DNA damage and mutations (78). The guanine base in DNA has the highest susceptibility to the formation of MDA adducts and therefore the MDA-reacted DNA is generally detected in a form of MDA-deoxyguanosine (79). Furthermore, it has been demonstrated that MDA inhibits DNA damage repair mechanisms (80). In this context, although MDA is less toxic compared with 4-HNE, which is the most toxic lipid peroxidation product, it still has potent mutagenic activity (81).

4. ALDH1A1 in cancer

ALDH1A1 is generally considered to be a marker of CSCs, and elevated ALDH1A1 expression is generally associated with increased malignant behaviors and therapy resistance in cancer (82). Although the antitumor activities of ALDH1A1 have been demonstrated in some types of cancer (or some conditions in cancer), it is generally accepted that it is involved in the regulation of multiple mechanisms to promote cancer progression (83).

ALDH1A1 promotes stemness and therapeutic resistance mainly by being involved in RA synthesis (84). In this sense, as aforementioned, reactive aldehydes are detoxified during

RA synthesis. In addition, synthesized RA induces signaling mechanisms such as PI3K/AKT, Wnt/β-catenin and Notch, which stimulate the activity of several transcription factors that promote stem cell behavior, and various ABC family transporter proteins that are directly involved in drug resistance (85,86). Consequently, elevated ALDH1A1 activity results in an increase in CSCs, and promotes therapy resistance and tumor recurrence (87-89). One important self-limiting factor against ALDH1A1-overexpressing tumors is the impact of RA on cell physiology; specifically RA induces differentiation to a number of cell types, such as normal stem cells or acute promyelocytic leukemia cells (1), thus making ALDH1A1 an attractive intervention target since in those cell types both exogenous RA and endogenous ALDH1A1 activity, which generates RA, limit their proliferation; by contrast, in cells insensitive to RA, ALDH1A1 inhibition decreases CSC frequency (1).

ALDH1A1 in BCa. ALDH1A1 upregulation has been associated with higher grade tumors and increased malignancy in patients with BCa (90). It has been reported that patients with ALDH1A1 (+) non-triple-negative BCa (TNBC) tumors have a shorter survival time compared with that of patients with ALDH1A1 (-) tumors (91). Notably, ALDH1A1 positivity has been reported as a signature for early relapse and a more aggressive phenotype in patients with ER (+)/HER2 (-) BCa (92). In the context of TNBC, it has been reported that ALDH (+) cells are enriched in TNBC cell lines compared with in non-TNBC cell lines (93), and ALDH1A1 positivity is an independent prognostic factor in TNBC (94). Furthermore, an association between ALDH1A1 positivity and tumor grade, ER/progesterone receptor (PR) negativity and HER2 positivity has been reported (90,95), and it has been shown that ALDH1A1 expression is higher in ER/PR (-) and HER2 (+) tumors that have high Ki67 levels in patients with BCa (96). Numerous studies have reported that ALDH1A1 positivity could be an independent marker of poor prognosis in patients with luminal or TNBC tumors (97-102); however, although ALDH1A1 positivity in tumor cells is important for predicting prognosis in BCa, serum ALDH1A1 has been reported to be inappropriate as a marker (103). Notably, high ALDH1A1 expression in stromal cells of TNBC tumors has been reported to predict a favorable prognosis in BCa (104).

At least in normal epithelial cells, the effects of ALDH1A1 on stemness can be attributed to RA. The use of fluorescence-activated cell sorting of primary human mammary epithelial cells, along with *in vitro* and *in vivo* functional assays to examine the relationship between cells with ALDH enzymatic activity ($ALDH^+$ cells) and ER^+ cells in the normal human breast epithelium, demonstrated that ALDH1A1 knockdown could significantly reduce the number of primary and secondary mammospheres formed in suspension culture and that this effect could be rescued by RA. Notably, this approach dissociated between the effects of ALDH1A1 on mammospheres and proliferation, as RA (produced by ALDH1A1) resulted in a block in proliferation, whereas ALDH1A1 was shown to have an important role in the formation of mammospheres (105). In this study it was shown that ER^- cells gave rise to ER^+ cells; the ER^- cell population contains

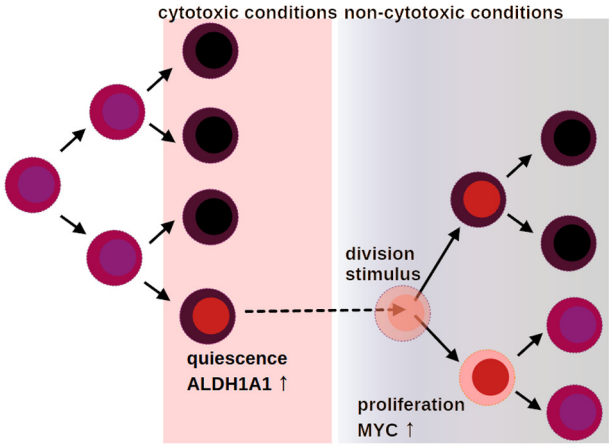

Figure 1. Proliferating cancer cells may be killed under cytotoxic conditions. Under those conditions, cells that enter a dormant state with regard to cell proliferation and metabolism appear to be protected. Expression of ALDH1A1 can protect quiescent or slow-cycling cells that express lower levels of antioxidant system enzymes. Exposure to altered conditions and to increased nutrients may trigger proliferation and metabolism in primed cancer cells, especially after stimulation by a variety of signals that include inflammatory agents, which induce MYC expression through induction of NFκB transcriptional activity. Cells with decreased protection from oxidative stress may die under those conditions. ALDH, aldehyde dehydrogenase.

a subset of cells that can generate ER^+ cells, which are able to proliferate proving that ALDH1A1 expression is consistent with stem cell function, since ER^- (ALDH1A1 expressing) cells generated ER^+ cells, in the same manner that stem cells generate both proliferating and differentiating cells (105). This is noteworthy because in a later study, $ALDH^+$ BCa CSCs were shown to include both quiescent as well as proliferating clones, suggesting the role of ALDH activity as a viability safeguard during the phenotypic transitions of malignant stem cells, which permits them to generate diverse subclones with variable adaptation potential; single-cell RNA profiling previously identified a dormant $ALDH^+$ population that expanded after anti-estrogen treatment (106). Anti-estrogen treatment led to expansion of the quiescent clones, which supports the hypothesis that quiescence is a mechanism of malignant cell adaptation to antineoplastic treatment; under conditions that trigger cell death or cell cycle arrest, the cells that enter a dormant state in respect to cell growth and metabolism appear to be protected (Fig. 1). Exposure to a number of cytotoxic and cytostatic agents may favor the growth of clones that have adaptive mechanisms; for example, tamoxifen treatment has been shown to induce ALDH1A1 expression in breast cancer cells expressing the ER variant ERα36, and these cells have the capacity for proliferation and metastasis in BALB/c nude mice (107).

The effect of ALDH1A1 on stemness via RA production may also be associated with SRC-3, a steroid receptor co-activator, which is a critical factor in the development and progression of BCa (108). SRC-3 interacts with RA-activated RARα and regulates RARα transcriptional activity (109). Conversely, RA also promotes the phosphorylation and ensuing ubiquitin-dependent proteasomal degradation of SRC-3 in a p38/Cul3-dependent manner and this event contributes to an anti-proliferative effect of RA (110). In this manner, RARα transcriptional activity is regulated by SRC-3 under the control

of RA and p38/Cul3 (110,111). However, RA has been reported to induce SRC-3 phosphorylation and degradation only in $HER2^-$ cells, such as MCF-7, but not in $HER2^+$ cells, such as BT474 and MDA-MB-361 cells (110). Therefore, due to the different molecular contents of tumor cells, the increase in the amount of RA produced due to upregulation of ALDH1A1 will not have the same effect on every cell. Although erbB-2 expression is apparently a critical factor that determines the mechanism of cell response to increased ALDH1A1 activity and RA production, there may be more contributing factors that remain to be defined. In the context of CSCs, SRC-3 has been implicated in the induction and maintenance of breast CSCs (112). Notably, SRC-3 (but not SRC-1 or SRC-2) silencing by small interfering (si)RNA or inhibition using the chemical inhibitor SI-2 in $HER2^+$ and TNBC BCa cell lines has been shown to lead to a decrease in ALDH activity and in $ALDH^+$ cell populations (112).

While estrogen alone induces BCa cell proliferation, RA generally inhibits cell proliferation through multiple mechanisms including interactions between different proteins of the RA and estrogen signaling pathways (113,114). Notably, the effects of RA on BCa cells are generally regulated by a crosstalk between ER and RAR signaling mechanisms (115). In addition, ATRA inhibits the proliferation of ER (+) BCa cells, but not of ER (-) cells (116); however, at the genomic level, the interaction between RAR and ER signaling mechanisms is complex. RARα is an estrogen-regulated gene that is associated with ER expression in BCa (117). In addition, RARα and ER share common cis-regulatory elements in the genome, and RARα interacts with ER during estrogen stimulation and regulates the transcription of ER target genes as part of a joint RAR/ER transcriptional complex (64). However, the scenario in which ER and RAR interact in the presence of estrogen and bind to the promoter of target genes as a transcriptional complex may change when RA is also present. It has been reported that in some cases of BCa, ER and RAR can compete with each other to bind to regions of the genome where they recognize common target DNA sequences, that ER signaling can be inhibited in the presence of RARα ligands, and conversely that RAR signaling can be suppressed by the presence of estrogens (118). For example, estradiol (E2) treatment has been shown to lead to protein kinase A-mediated lysine-specific histone demethylase 1 (LSD-1) activation and thereby to demethylation of H3K9me2, resulting in the joint binding of ERα and RARα to the promoter of target genes such as BCL-2 (119). However, RA inhibits E2-induced LSD-1 activation, preventing H3K9me2 demethylation and consequently suppressing this part of estrogen signaling (119). In the context of high ALDH1A1 expression in BCa, high ALDH1A1 levels may result in more RA production, which could then inhibit cell proliferation by blocking ER-mediated signaling by binding to regions of the genome where ER and RAR can bind together. However, the proposed mechanism is based on the currently available literature and it is possible that other parameters of this relationship may also emerge due to genomic, transcriptomic/proteomic and metabolomic differences in different subsets of BCa.

ALDH1A1 promotes the invasion and metastasis of BCa (120). By contrast, ALDH1A1 depletion inhibits metastatic behavior (121). In invasive BCa, ALDH1A1 expression has been reported to be higher in invasive components when compared with *in situ* components (122). It has been shown that the presence of ALDH1A1 (+) cells in lymph node metastases after chemotherapy is associated with an unfavorable prognosis (123). In cancer cells, the association between EMT/stem cell marker expression and radiotherapy/chemotherapy resistance, and their effects on metastasis processes are well known (124). In addition, circulating tumor cells (CTCs) that have EMT and CSC features, generally predict chemotherapy resistance and poor prognosis in patients with BCa (125). Therefore, ALDH1A1-induced invasion and metastasis may be associated with its probable relationship with EMT, at least in part. EMT is a phenotypic adaptation mechanism that provides flexibility to cells, allowing them to perform new functions. Although EMT can manifest in normal physiological processes, such as embryonic development, it is generally associated with increased malignant behaviors in cancer cells, and with poor prognosis in patients with solid tumors or hematological malignancies (43,126-128). Notably, an association has been reported between ALDH1A1 and vimentin/fibronectin levels in CTCs from patients with BCa (129). Similarly, it has been reported that CTCs with high ALDH1A1 expression generally have high vimentin and TWIST1 expression (130). In addition, CTCs from patients with BCa that have both high ALDH1A1 expression and nuclear TWIST1 localization have a higher metastatic potential (131). Although it is not yet known whether it directly binds to the promoter of the ALDH1A1 gene, TWIST1 has been shown to positively regulate ALDH1A1 expression in breast CSCs (132). In this sense, although there are clues for a possible association between TWIST1 and ALDH1A1 expression, it has not yet been clarified. A study conducted in primary and metastatic BCa tumors investigated the possible relationship between ALDH1A1 and EMT-inducing transcription factor expression, and it was reported that patients with ALDH1A1 and Snail 2 (Slug) co-expression in their primary tumors have a shorter disease-free survival (133). ALDH1A1 may also induce angiogenesis through the RA/HIF-1α/VEGF signaling axis in BCa cells (134).

A critical observation that has been made in BCa is that CD44 (+)/ALDH1A1 (+)/Ki-67 (-) tumor cells may favor distant metastasis and predict poor overall survival in patients with ductal carcinoma *in situ* (135). In this previous study, quiescence of breast CSCs was shown to be associated with tumor progression, treatment resistance and metastatic capacity. Quiescence can protect stem cells in general by decreasing the generation of reactive oxygen species (ROS) through a lower metabolic rate, since it has been shown that quiescence of hematopoietic stem cells protects them from DNA damage (136-139). Support for this hypothesis was provided when reviewing information from previously published studies, including studies conducted with samples from healthy volunteers, as well as studies with samples from patients with cancer, including primary cancer samples from the Genomic Data Commons-deposited data of The Cancer Genome Atlas BRCA study (Table I).

When the correlation between mRNAs extracted from healthy volunteers and patients is taken into consideration, three trends appear regarding the mRNA expression of MYC, ALDH1A1 and ALDH2: i) The two ALDH genes are correlated

Table I. A review of the correlations of the mRNA expression levels of MYC, ALDH1A1 and ALDH2, and HRD determined in published studies, via the online platform Xena.

Variable 1	Variable 2	Study	Units of RNA	Number of samples	Correlation r-vaue	P-value
ALDH2	MYC	GTEX	log2(norm_count +1)	9,783	-0.02	0.027
ALDH1A1	MYC	GTEX	log2(norm_count +1)	9,783	-0.09	$1.20x10^{-16}$
ALDH1A1	ALDH2	GTEX	log2(norm_count +1)	9,783	0.42	0
ALDH2	MYC	GTEX, filter: 'blood'	log2(norm_count +1)	1,348	-0.29	$3.40x10^{-23}$
ALDH1A1	MYC	GTEX, filter:'blood'	log2(norm_count +1)	1,348	-0.32	$7.50x10^{-28}$
ALDH1A1	ALDH2	GTEX, filter:'blood'	log2(norm_count +1)	1,348	0.79	$4.30x10^{-226}$
ALDH2	MYC	GDC PAN CANCER	log2(fpkm-uq +1)	14,741	-0.078	$9.90x10^{-16}$
ALDH1A1	MYC	GDC PAN CANCER	log2(fpkm-uq +1)	14,741	-0.11	$6.00x10^{-31}$
ALDH1A1	ALDH2	GDC PAN CANCER	log2(fpkm-uq +1)	14,741	0.49	$<10^{-250}$
ALDH2	MYC	TCGA & TARGET	log2(norm_count +1)	18,802	-0.11	$1.00x10^{-31}$
ALDH1A1	MYC	TCGA & TARGET	log2(norm_count +1)	18,802	-0.09	$2.90x10^{-24}$
ALDH1A1	ALDH2	TCGA & TARGET	log2(norm_count +1)	18,802	0.48	$<10^{-250}$
ALDH2	MYC	TCGA primary cancer	log2(norm_value +1)	10,804	-0.07	$1.70x10^{-12}$
ALDH1A1	MYC	TCGA primary cancer	log2(norm_value +1)	10,804	-0.13	$9.60x10^{-40}$
ALDH1A1	ALDH2	TCGA primary cancer	log2(norm_value +1)	10,804	0.45	$<10^{-250}$
ALDH2	HRD	TCGA primary cancer	log2(norm_value +1)	10,804	-0.19	$1.46x10^{-86}$
ALDH1A1	HRD	TCGA primary cancer	log2(norm_value +1)	10,804	-0.13	$3.40x10^{-40}$
MYC	HRD	TCGA primary cancer	log2(norm_value +1)	10,804	0.2	$6.30x10^{-94}$

Pearson correlation values are shown, with corresponding Spearman correlation values provided in the Xena platform (https://xenabrowser.net/). HRD refers to genome-wide DNA damage footprint. ALDH, aldehyde dehydrogenase; GDC, Genomic Data Commons; GTEX, Genotype-Tissue Expression; HRD, homologous recombination deficiency; TCGA, The Cancer Genome Atlas.

at the mRNA level, indicating that cells tend to express similar levels of ALDH1A1 and ALDH2; ii) the two ALDH genes are either not correlated, or even inversely correlated with MYC; and iii) the two ALDH genes are either not correlated, or even inversely correlated with cellular DNA damage, as indicated by the homologous recombination deficiency (HRD) score, whereas the opposite occurs with MYC RNA: MYC RNA is correlated with the DNA damage index (HRD score), which may reflect increased metabolic activity of cells that generate ROS to the extent that leads to DNA damage. Therefore, ALDH1A1 and ALDH2 RNA tend to be expressed more under conditions not conducive to cellular DNA damage. This is consistent with their increased importance for slower cell growth states. Such slower growth may also correspond to some forms of dormant growth arrest that places limits to DNA damage (138,140,141). The platform used for extracting the information shown in Table I was University of California, Santa Cruz Xena (https://xenabrowser.net/) (142). This concise overview of previous studies supports the hypothesized role of ALDH1A1 in quiescent stem cells, and suggests that ALDH1A1 has an important role in quiescent CSCs, which is consistent with the aforementioned role of ALDH1A1 in mammospheres (105).

Regarding how aggressive cancer cells arise from quiescent cells, cell quiescence can still result in aggressive cancer after relapse due to the aberrantly exposed chromatin on certain key genes in CSCs, such as MYC, which permit rapid phenotypic changes under favorable conditions (51,143). A more precise association of the function of each gene can only be made after considering the impact of the gene product under different conditions *in vitro* and *in vivo*, and after factoring the hazard ratio of the expression of the gene for different patient groups.

Any hypothesis that is solely based on the measurements of RNA steady-state levels can only have a theoretical value in the absence of mechanistic studies in cultured cells. Results as those shown in Table I can easily become irrelevant in data-sets obtained from slightly different sample types. Thus it is important to bear this in mind until multiple types of analysis support this hypothesis.

A key recent discovery enabled tracking of CSCs in BCa with a reporter system using a far-red fluorescent protein under the control of the ALDH1A1 promoter. Positively stained cells have been shown to exhibit stemness characteristics that include higher sphere-forming capacity, tumor formation and increased resistance to anticancer treatments (144). Notably, live tracking of cells in a microfluidic system has revealed a higher extravasation potential of CSCs, and for the first time, the live reprogramming of non-CSCs into CSCs (144). This reprogramming that facilitates interconversion between CSCs and non-CSCs can explain why ALDH1A1-positive CSCs may prove far more elusive than anticipated, especially in light of a recently discovered variability in the effects of RA-binding proteins on the capacity for proliferation and drug resistance of BCa cells (145). One interesting approach to assess the complexity of RA effects is to design interventions that selectively target intracellular RARγ; if this has similar results to

knocking out or inhibiting ALDH1A1, it may be hypothesized that RARγ mediates the effects of ALDH1A1 on CSCs (146).

ALDH1A1 in other types of cancer. In lung cancer ALDH1A1 levels are high in both non-small cell lung cancer (NSCLC) and SCLC compared with in normal healthy cells, and much higher in NSCLC compared with in SCLC (147). ALDH1A1 has been shown to promote cell cycle arrest by inhibiting the Notch/CDK2/Cyclin E pathway in lung cancer cells, thus improving clonogenic abilities and stemness (148). Notably, ALDH1A1 expression has been reported to be higher in advanced-stage lung tumors and cisplatin-resistant lung cancer cells compared with in early-stage tumors and cisplatin-sensitive cells, and ALDH1A1-depleted cells are sensitive to cisplatin (149,150). In addition, inhibition of ALDH1A1 activity using a disulfiram/copper complex can suppress the malignant behaviors and relapse of NSCLC (151). Therefore, ALDH1A1 expression has been proposed to be associated with poor prognosis in patients with NSCLC (152-154). Furthermore, the S100A9/ALDH1A1/RA pathway has been reported to promote metastatic brain relapse in patients with EGFR-mutant lung cancer treated with the EGFR tyrosine kinase inhibitor osimertinib, whereas targeting of S100A9, RAR or ALDH1A1 may inhibit brain metastasis in these patients (155).

It has also been suggested that ALDH1A1 may act as a tumor suppressor in NSCLC, especially in smokers (156). Although a mechanistic explanation has not been provided in this study, a recent study revealed that patients with lung cancer lacking ALDH1A, CD133 and mutant p53 have a better prognosis (157). Therefore, the results of Okudela *et al* (156), which do not comply with the existing literature, may hint to a tumor-suppressing impact of ALDH1A1-generated RA. This situation also shows that a number of molecules may be involved in the downstream effects of ALDH1A1 on tumorigenesis. Another likely explanation is that the proportion of ALDH1A1-positive lung cancer stem-like cells is low in aggressive tumors. As mentioned in the present review, one explanation that should be considered for solid tumors, is that when ALDH1A1 activity causes an increase in RA, activated RARs confer a positive disease outcome by leading to the suppression of aggressive tumors through a number of different mechanisms (158). This suppression can be in part attributed to an increase in differentiated cell phenotypes (159). Moreover, ectopic expression of the RA-induced G gene (also known as IFIT3) has been shown to lead to a significant decrease in the proliferation of lung cancer cells, resulting in an inhibition of tumor xenograft growth in mice (160). Solid tumor cells derive from non-circulating cell clones that in general do not adapt to drastic changes in their microenvironment; therefore the influence of local gradients of RA during primary cancer growth should be significant and affect the disease course. It must also be noted that RAR competes with the vitamin D receptor for RXR binding and for interference with RXR signaling (161), which adds a substantial degree of flexibility for RA signaling and its downstream effects. In particular, these interactions may have an important role in restoration and maintenance of epithelial barrier function; while this has been suggested for intestinal tissue it is very likely to apply for other types of epithelial tissue as well (162).

In prostate cancer (PCa), it has been reported that a relationship exists between ALDH1A1 expression levels and Gleason score, and that ALDH1A1 expression is higher in castration-resistant PCa compared with in castration-sensitive PCa (163). Notably, increased ALDH1A1 expression is associated with metastasis and poor prognosis in PCa (164); however, increased ALDH1A1 expression in stromal cells adjacent to cancer cells is associated with a better prognosis, similar to in BCa (165). ALDH1A1 expression has also been shown to be associated with resistance to radiotherapy (41). In PCa, among other effects, ATRA treatment suppresses ALDH1A1 expression, activates CDK5 and increases p27 levels in androgen receptor-negative cells, thereby inhibiting proliferation (166). This could make ALDH1A1 expression self-liming under certain conditions of slow ATRA turnover, particularly in tumors where oncogenic RA signaling pathways, such as RARγ, do not prevail over tumor-suppressing mechanisms (146).

In ovarian cancer, high ALDH1A1 levels are associated with chemotherapy resistance and poor prognosis (167). Notably, an association has been identified between high ALDH1A1 expression levels and shorter overall survival (168). In this context, ALDH1A1 alters the signaling network in cell cycle checkpoints and DNA repair processes, and thereby maintains ovarian CSCs (169). ALDH1A1 levels are increased after neoadjuvant treatment, and this event is associated with chemoresistance and poor prognosis (170). The levels of ALDH1A1 and several drug transporter proteins are high in paclitaxel- and topotecan-resistant ovarian cancer cells, and ATRA treatment can decrease both ALDH1A1 and drug transporter protein levels leading to a decrease in the resistance to chemotherapy agents (171). However, ALDH1A1 depletion in topotecan- and paclitaxel-resistant ovarian cancer cells results in an increase in paclitaxel resistance, although it causes a decrease in topotecan resistance (172). Inhibition of ALDH1A1 activity can both diminish the CSC population and inhibit cisplatin-induced senescence that would otherwise promote stemness via paracrine signaling (173). Consequently, co-expression of ALDH1A1 and SALL4 in patients with serous ovarian cancer is associated with an overall unfavorable prognosis (174).

A negative association has been demonstrated between high ALDH1A1 RNA expression and overall survival in patients with acute myeloid leukemia (AML) (175). Notably, it has previously been shown that ALDH1A1 RNA-null patients belong to the AML favorable prognosis risk group (176). These findings suggest that ALDH1A1 is a potential target for AML treatment. One compound that targets ALDH1A1 and possibly other similar enzymes is DIMATE (177,178), which is currently under study for AML in the phase 1 clinical trial 'ODYSSEY' (NCT05601726) for patients with relapsed AML (179,180).

Disulfiram is a Food and Drug Administration (FDA)-approved drug that, among a number of other targets, inhibits ALDH1A1 at sub-micromolar concentrations (181). Disulfiram specifically targets CSCs in AML by increasing activity of the ROS-induced JNK pathway and by inhibiting the NFκB and Nrf2 pathways (182). Furthermore, elevated ALDH1A1 expression is associated with sorafenib resistance in various types of cancer, including AML (183). This suggests that, at least for AML, preclinically targeting ALDH1A1 is an

option worth considering. Notably, AML cells can escape the downstream effects of RA production. In the normal human bone marrow, mesenchymal cells prevent retinoid-induced differentiation of hematopoietic stem cells by maintaining a low RA concentration, via CYP26-mediated degradation (184,185). However aggressive AML cells can be expected to adapt to a RA-rich microenvironment, and thereby tolerate high levels of ALDH1A1 expression and activity (82). This aberration renders a substantial portion of AML cells highly resistant to RA (186). However conversely, this discovery leads to the expectation that AML cells resistant to RA can be killed by inhibition of ALDH1A1, since ALDH1A1 protects them from cytotoxic aldehydes. This RA insensitivity brings AML into sharp contrast with BCa, since at least a notable part of BCa cells contains functional RARα and RARγ, and responds to RA; this at least applies to cytokeratin 5-positive BCa cells, which are the most aggressive malignant cells (187). ALDH1A1-overexpressing BCa cells would therefore be expected to thrive mostly in association with stromal cells that remove RA; stromal cells metabolize RA and decrease exposure of BCa cells to RA; therefore, interfering with stromal cells may aid the development of experimental therapeutic approaches.

Another pathway for the cancer-supporting effects of ALDH1A1 has been discovered in multiple myeloma cells, where ALDH1A1-generated 9-cis RA activates RXR to induce NIMA-related kinase 2 (NEK2) expression; this has been shown to increase clonogenicity and tumorigenicity, and additionally cause resistance to two widely used myeloma drugs (bortezomib and doxorubicin) by enhancing expression of the drug-efflux pump ABCB1 and of survival proteins, AKT and BCL-2 (188). NEK2 activation in multiple myeloma is important, since it also activates autophagy (via the lysosome), which helps malignant cells survive for several reasons in addition to the most obvious reason, which is resistance to proteasome inhibition (189). The discovery of the effect of ALDH1A1 on NEK2 may also be relevant in BCa, since NEK2 has been shown to control proliferation, migration, invasion and viability of cultured BCa cells (190).

The positive association between ALDH1A1 expression/activity and tumorigenesis, poor prognosis and therapy resistance is not limited to the aforementioned types of cancer, and has also been demonstrated in a number of other types of cancer, including bladder, colorectal, head and neck, esophageal and gastric cancer (191-196). In comparison to other CSC markers, ALDH1A1 expression in adenocarcinoma appears to have a stronger association with tumor initiation, asymmetric division and interconversion between cellular phenotypes, properties that are consistent with increased flexibility during critical phases of cancer progression (197). The net effect of the expression of ALDH1A1 in the different cell types of a given tissue depends on the interactions of its reaction products with diverse signaling pathways, which include, but are not limited to, nuclear receptor-activated cascades. Notably, in addition to the detoxification of aldehydes, ALDH1A1 can contribute to drug resistance in several other manners, such as via the expression of drug transporter proteins and of antiapoptotic factors, in addition to the activation of autophagy, most of these effects are also paradoxically linked to the generation of RA, due to differential activation of RA-dependent pathways; therefore increases in ALDH1A1 activity and RA concentration elicit fundamental alterations in cell signaling mechanisms that affect how the cells respond to stimuli and whether cells proliferate, differentiate or die. Specifically, cells that express RARα may differentiate upon increased ALDH1A1 activity that generates RA, while cells deficient in RARα are in position to resume proliferation once the cell microenvironment transitions from cytotoxic to non-cytotoxic conditions that provide additional stimuli, which induce cell division (Fig. 2).

5. ALDH1A1 contributes to therapeutic resistance via multiple means in BCa

There is a clear negative association between ALDH1A1 levels and treatment success in BCa. Notably, high ALDH1A1 expression results in resistance to numerous chemotherapeutic drugs that use different cellular mechanisms to exert their antineoplastic effect. This makes ALDH1A1 an important target in the treatment of BCa.

ALDH1A1 is involved in cyclophosphamide resistance and a decrease in ALDH1A1 expression is important in the success of cyclophosphamide treatment in BCa (13). It has been reported that ALDH1A1 levels are lower in BCa cells that respond to cyclophosphamide compared with in cells that do not respond to this treatment (198). Similarly, it has been shown that ALDH1A1 positivity is associated with poor clinical outcome and prognosis in cyclophosphamide-treated patients (199). Furthermore, ALDH1A1 levels are higher in metastatic BCa cells treated with cyclophosphamide compared with in cells not exposed to cyclophosphamide (198), and an increase in cytoplasmic β-catenin levels along with an increase in ALDH1A1 levels is associated with poor prognosis in patients receiving cyclophosphamide treatment (200). In a recent study, raloxifene and bazedoxifene were identified as selective ALDH1A1 inhibitors by using virtual screening approaches, and it was shown that both compounds can increase the sensitivity of ALDH1A1-overexpressing cells to mafosfamide sodium salt, a cyclophosphamide analog (201). Ifosfamide is another oxazaphosphorine group chemotherapeutic drug like cyclophosphamide, and ALDH1A1 has been shown to detoxify it as well (202). In a recent study, telmisartan, irbesartan and maraviroc were reported as prospective ALDH1A1 inhibitors by the use of computational approaches, although experimental evidence was not provided (203).

As aforementioned, disulfiram is an FDA-approved substance for individuals wishing to abstain from alcohol, and it is also a prospective antineoplastic drug that seems to be a promising molecule for inhibition of ALDH1A1 (204). Notably, disulfiram/copper complexes have been reported to decrease NFκB activity, increase total ROS levels and MAPK signaling activity, and inhibit malignant behaviors in BCa cells (205). In addition, disulfiram inhibits HER2/AKT signaling and suppresses stemness in HER2 (+) BCa cells (206). Disulfiram also inhibits STAT3 signaling, and thereby decreases cyclin D1 and survivin levels, in addition to inhibiting ALDH1A1 activity in TNBC (207). In this context, STAT3 signaling may be a critical pathway for the regulation of ALDH1A1-induced stemness and malignant behaviors in BCa. Notably, STAT3 activity is higher in ALDH (+) BCa cells compared with in ALDH (-) cells and inhibition of STAT3 activity using a

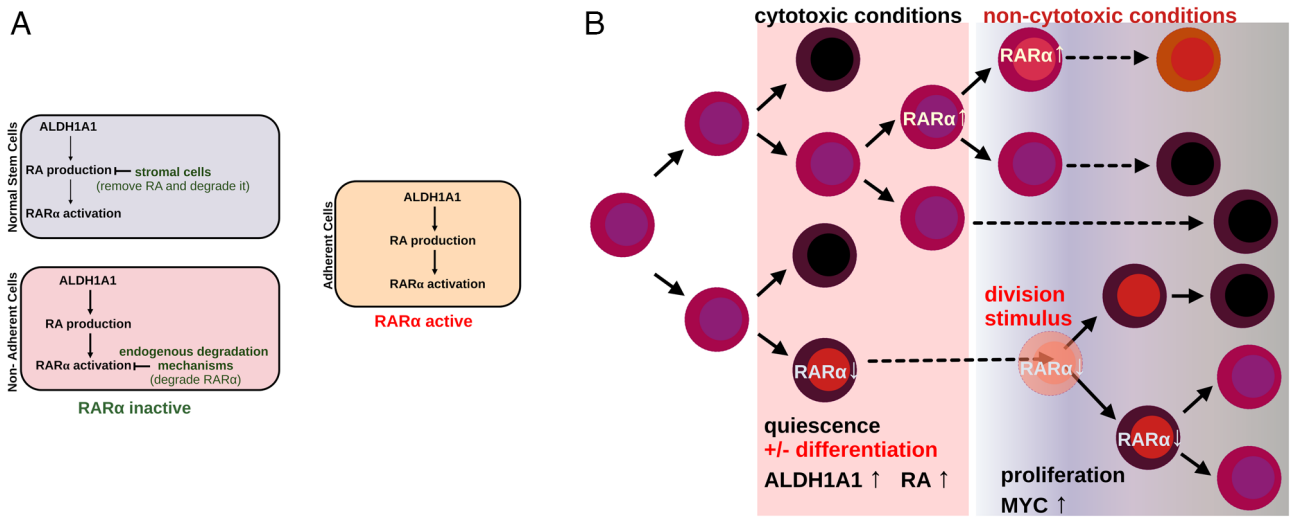

Figure 2. A model for cancer evolution based on the status of RARα; cells respond differently to cytotoxic conditions and to differentiation stimuli depending on which RAR they express, and also depending on how much RA they are exposed to. (A) RARα is not activated in normal stem cells despite their ALDH1A1 activity because stromal cells remove RA and degrade it. Circulating cells operate proteolytic systems, such as proteasomal and lysosomal degradation that may degrade RAR; therefore, RAR signaling cannot be activated even if cells overexpress ALDH1A1 enzymes. Adherent cells are less likely to degrade RAR under physiological conditions, and so the adherent cells respond to RA based on their relative expression levels of RARs. Both RA and RAR are subject to degradation by different cell types, and this largely determines tumor response to ALDH1A1 activity. (B) Cancer cells that express RARα differentiate, while those that do not may continue to proliferate despite the increased exposure to RA. ALDHA1, aldehyde dehydrogenase A1; RA, retinoic acid; RARα, retinoic acid receptor α.

chemical inhibitor can both suppress the ALDH (+) cell population and inhibit tumor growth (208). A novel ferrocene derivative synthetic compound has been reported to inhibit both mammosphere formation and stem cell properties, including downregulation of ALDH1A1 expression, in BCa cells through ROS production and STAT3 inhibition (209). Dinaciclib, a CDK1/2/5/9 inhibitor, decreases ALDH1A1 levels along with the levels of pluripotency-associated transcription factors, including NANOG, OCT4 and SOX2. This effect of dinaciclib has been attributed to inhibition of FoxM1 in a sonic hedgehog-dependent manner (210). However, more recently it was shown that in AML cells dinaciclib inhibits STAT3 activity in an ERK-dependent manner and consequently decreases Myc expression (211). Although it is not yet known whether the effect of dinaciclib causing the decrease in ALDH1A1 levels is dependent on STAT3, it may be at least a viable working hypothesis, although AML is a different study system from BCa. In addition, it has been shown that esculentoside A inhibits mammosphere formation and the proliferation of breast CSCs, decreases ALDH1A1, SOX2 and OCT4 levels and STAT3 activity, and induces apoptosis (212). In summary, STAT3 activity may be important in the control of ALDH1A1 levels, and ALDH1A1 is associated with malignant behaviors and therapy resistance in BCa.

It has been shown that although tamoxifen and fulvestrant decrease total BCa cell proliferation, they nevertheless increase breast CSC activity in a Notch-dependent manner (213). In addition, it has been demonstrated that ALDH1A1 levels are increased in the tumors of patients with ERα (+) BCa and disease relapse after surgery and tamoxifen treatment (214). Notably, ALDH1A1 is a tamoxifen-responsive gene: Tamoxifen induces ERα-36, a variant of ERα, to translocate to the cell nucleus, where it directly binds to the ALDH1A1 promoter (107), and consequently, increased ALDH1A1 levels promote metastasis and stemness. In addition, the use of ALDH1A1 inhibitors or ERα-36 antibodies has been shown to abolish the effects of tamoxifen-induced malignant behaviors (107).

A negative association has been reported between ALDH1A1 expression and neoadjuvant therapy response in BCa (215,216) and it has been shown that an increase in ALDH1A1 levels after neoadjuvant therapy may be a predictor of a weaker therapeutic response (217). Consequently it has been proposed that ALDH1A1 expression may be used to monitor neoadjuvant chemotherapy success (199).

CYP2J2-overexpressing BCa cells are generally resistant to chemotherapy agents and it has been shown that ALDH1A1s levels are also high in these cells, and that resistance to chemotherapy agents is mainly regulated by inhibiting the chemotherapy-mediated ROS production by ALDH1A1, thus protecting the cells from death (218). Therefore silencing of ALDH1A1 may be a practical approach to overcome chemotherapy resistance in CYP2J2-overexpressing BCa cells.

Various plant-derived molecules have been shown to reduce ALDH1A1 activity/expression, thereby sensitizing BCa cells to chemotherapy. For example, curcumin and curcumin derivative synthetic analogues can decrease ALDH1A1 levels in breast CSCs (219,220); this effect is dependent on the sonic hedgehog and Wnt/β-catenin pathways (221). Therefore, curcumin and its derivatives may be considered as candidate agents for the purpose of overcoming drug resistance in BCa. A combined curcumin and vitamin D treatment has been shown to increase sensitivity to paclitaxel, as well as the apoptotic potential, and to decrease ALDH1A1 levels in paclitaxel-resistant BCa cells (222). In this context, curcumin-dependent inhibition of ALDH1A1 may be a useful approach to overcome paclitaxel and epirubicin resistance, since ALDH1A1 is a reliable biomarker for paclitaxel and epirubicin resistance in breast CSCs (223).

Quercetin has also been shown to suppress the malignant behaviors of breast CSCs and to induce apoptosis via inhibition of ALDH1A1 along with CXCR4, MUC1 and EpCAM (224). It was also shown that sulforaphane inhibits TNBC tumor development in an animal model and that it decreases the expression of various stem cell markers, including ALDH1A1, via a Cripto-mediated pathway (225). In addition, it has been reported that sulforaphane decreases the ALDH1A1 (+) cell population in both TNBC and ER (+)/PR (+) BCa cells (226). Furthermore, 4-vinylphenol decreases ALDH1A1 levels, and inhibits sphere formation and malignant behaviors of CSC-enriched BCa cells via inhibition of EGFR/AKT/β-catenin signaling (227). Although this previous study did not provide a mechanistic explanation for the association between the decrease in ALDH1A1 and the inhibition of EGFR/AKT/β-catenin signaling, a similar mechanism has been observed in esophageal squamous cell carcinoma cells, where ALDH1A promotes both malignant behaviors and 5-FU chemotherapeutic resistance by activating AKT signaling and via interacting with β-catenin (228). Silybin is another plant-derived complex that inhibits ALDH1A1 expression and thereby inhibits the malignant behaviors of PCa cells (229). Although its relationship with ALDH1A1 has not been elucidated, *in vitro* studies have shown that silybin inhibits malignant activity in various types of cancer, including BCa, and that silybin enhances the sensitivity of BCa and ovarian cancer cells to cisplatin and doxorubicin (230,231).

A recent study has shown that ALDH1A1 inhibits ferroptosis that is triggered by KRAS inhibitors and thereby leads to resistance to those agents that target KRAS (232). Although KRAS mutations are not common in BCa, it is known that mutated KRAS is associated with metastatic behavior and poor prognosis in BCa (233). Mutated KRAS promotes chemoresistance via increasing Nrf2 expression; in concordance, inhibition of the Nrf2 pathway can suppress KRAS-induced chemoresistance (234). In this context, it has been shown that ALDH1A1 activates Nrf2 in a p62-dependent manner (235).

Elevated ALDH1A1 expression has been reported to facilitate the entry of lysosomal autophagy inhibitors (including the chloroquine derivative hydroxychloroquine) into cells, resulting in increased cytotoxicity without affecting lysosome function or autophagic flux (236). Chloroquine is an anti-malarial drug and its repurposing as a cancer treatment has been discussed for years (237,238). Chloroquine targets CSCs by inducing mitochondrial damage and by impairing DNA break repair, in addition to inhibiting autophagy (239). In concordance, it has been shown that chloroquine encapsulated by a triphenylphosphonium-functionalized hyperbranched polymer results in a high cytotoxicity in mammospheres in an ATM-dependent manner (240,241). Therefore, the use of chloroquine or its derivatives in the treatment of cancer to target cells with high ALDH1A1 expression (in this case, mostly CSCs) may be a useful approach.

It may also be possible to specifically target CSCs by targeting ALDH1A1. Notably, it has been shown that ALDH1A1-specific $CD8^+$ T cells effectively target and suppress xenograft tumors and experimental metastases, in a study conducted for this purpose (242). This approach may be useful as a means to control the ALDH1A1-mediated tumor-promoting microenvironment in BCa. In this context, ALDH1A1 has been shown to trigger a molecular/metabolic cascade consisting of a decrease in intracellular pH, increased TAK1 phosphorylation and activation of NFκB signaling in tumor-initiating breast cells (243). This event results in increased granulocyte-macrophage colony-stimulating factor secretion from tumor-initiating cells (TICs) into the tumor microenvironment with the consequent expansion of myeloid-derived tumor suppressor cells (MDSCs) (243). Notably, the use of disulfiram (ALDH1A1 inhibitor) plus gemcitabine may inhibit tumorigenesis by targeting ALDH1A1 (+) TICs and activating T-cell immunity (243). The results of this previous study demonstrated a critical role of ALDH1A1 in the interaction between BCa-TICs and MDSCs during BCa progression, thus suggesting that a novel therapeutic approach targeting ALDH1A1 may be successful by disrupting this interaction in BCa.

6. Conclusion and perspective

The current literature indicates that at least some bulk tumor cells have the capacity to generate stem-like cells that act like CSCs, which can contribute to the progression of cancer and to therapy resistance. In the context of BCa, only a small fraction of malignant cells exhibit CSC characteristics and these cells generally have a high ALDH1A1 activity that is critical to the emergence of the CSC phenotype. As in other types of cancer, in BCa, decreasing ALDH1A1 expression via gene knockout or interference with gene expression, or inhibiting ALDH1A1 activity by using pharmaceutical agents, impedes the malignant behavior of cancer cells and contributes to overcoming treatment resistance. In this sense, ALDH1A1 may be an interesting and powerful target for cancer therapy.

In the context of BCa, it is notable that only a fraction of the malignant cells are expected to manifest stem-like features, including increased expression of ALDH1A1. Therefore, from the angle of disease prognosis, the extent of ALDH1A1 association with increased malignant behavior and drug resistance remains to be mapped by the application of cutting-edge methods that define the areas of the expression of biomarkers within tumors.

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LV, PZ, DAS, VZ and SV contributed to the conceptualization of the project, to the interpretation and analysis of data to be included in the review, and wrote and prepared the draft of the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Not applicable.

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Competing interests

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