Aldehyde dehydrogenases in cancer stem cells: potential as therapeutic targets

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Abstract: Resistance to current chemotherapeutic or radiation-based cancer treatment strategies is a serious concern. Cancer stem cells (CSCs) are typically able to evade treatment and establish a recurrent tumor or metastasis, and it is these that lead to the majority of cancer deaths. Therefore, a major current goal is to develop treatment strategies that eliminate the resistant CSCs as well as the bulk tumor cells in order to achieve complete disease clearance. Aldehyde dehydrogenases (ALDHs) are important for maintenance and differentiation of stem cells as well as normal development. There is expanding evidence that ALDH expression increases in response to therapy and promotes chemoresistance and survival mechanisms in CSCs. This perspective will discuss a paper by Cojoc and colleagues recently published in Cancer Research, that indicates ALDHs play a key role in resistance to radiation therapy and tumor recurrence in prostate cancer. The authors suggest that ALDHs are a potential therapeutic target for treatment prostate cancer patients to limit radiation resistance and disease recurrence. The findings are consistent with work from other cancers showing ALDHs are major contributors of CSC signaling and resistance to anti-cancer treatments. This perspective will address representative work concerning the validity of ALDH and the associated retinoic acid signaling pathway as chemotherapeutic targets for prostate as well as other cancers.

Keywords: Aldehyde dehydrogenase (ALDH); cancer; stem cells; retinoic acid signaling

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Solid tumors are composed of a variety of genetically distinct cancer cell types that are adapted to the conditions of the microenvironment. The majority of cells that comprise the tumor have limited capacity for self-renewal and are surprisingly, poorly tumorigenic. It is generally accepted that malignant tumors contain a small subpopulation of cells with stem cell properties (1,2). These cells, referred to as cancer stem cells (CSCs) or tumor initiating cells (TICs) are capable of evading current anti-neoplastic treatment regimens including chemotherapy and radiotherapy and dividing and differentiating into normal tumor cells after conclusion of treatment, leading to tumor recurrence or metastasis (2-4). This creates a serious problem with recurrent or metastatic tumors being responsible for most (≈90%) cancer deaths. The majority of current treatment strategies are based upon the clonal model of cancer and, therefore, target rapidly dividing cells leaving the quiescent and highly chemoresistant CSCs behind (*Figure 1*). This issue highlights the drastic need to develop new drugs and treatment strategies that can also target CSCs. Members of the aldehyde dehydrogenase (ALDH) family of proteins comprise a particularly interesting new class of potential targets. Humans have 19 ALDH proteins (5) and many have at least been determined to possess cancer-related

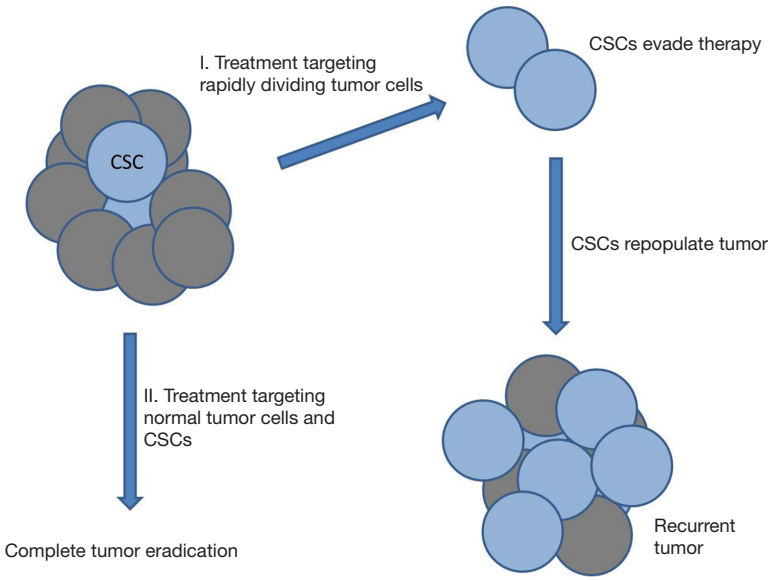

Figure 1 Treatment strategies for cancer. Current cancer treatment strategies (I) involve radiation or chemotherapeutic drugs that primarily target the differentiated, fast-growing cells that constitute the bulk of the tumor. CSCs frequently evade these treatments due to specific characteristics including quiescence, enhanced DNA repair, decreased ROS, and high levels of chemoresistance proteins (ALDHs and drug efflux pumps). Once treatment has ceased, the surviving CSCs can proliferate producing fully differentiated and more highly resistant tumor cells leading to disease recurrence. New treatment strategies (II) combine standard cancer treatments with drugs designed to either specifically target CSCs or that promote CSCs to differentiate into normal tumor cells which are then destroyed by standard treatment. This approach should allow the tumor to be completely resolved. CSCs, cancer stem cells; ALDH, aldehyde dehydrogenases; ROS, reactive oxygen species.

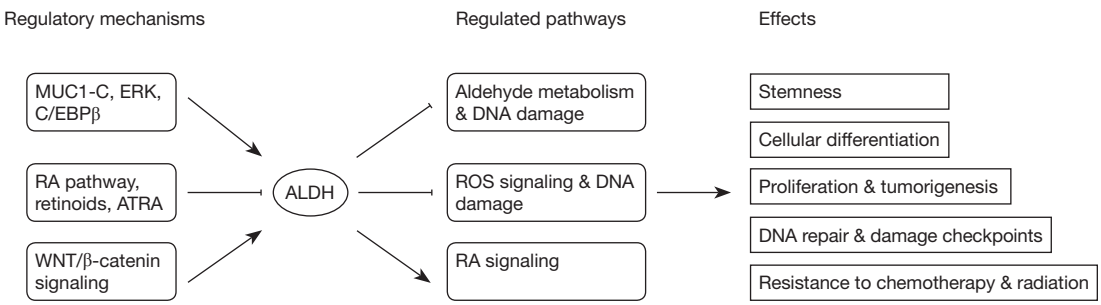

Figure 2 ALDHs regulate multiple pathways to contribute carcinogenesis and stem cell signaling. ALDHs are regulated by retinoic acid compounds including the chemotherapeutic retinoids and potentially oncogenic pathways such as WNT/β-catenin and MUC1-C/ERK. The ALDHs in turn oxidize aldehydes that participate in signaling mechanisms or induce cellular or DNA damage, minimize ROS production and mediate RA signaling cascades. These regulatory mechanisms combine to produce ALDH-mediated effects on cellular differentiation and proliferation, tumorigenesis, stemness and resistance to therapy. ALDH, aldehyde dehydrogenases; ROS, reactive oxygen species; ATRA, all-trans retinoic acid; ERK, extracellular signal-regulated kinase.

functions [reviewed in (6)]. ALDHs are spread throughout the body, catalyze oxidation of aldehydes and function in cellular detoxification, retinoic acid (RA) metabolism and signaling, development, protection from reactive oxygen species (ROS), and maintenance of the eye and vision (7-11). Many ALDHs have been implicated in stem cell regulation where ALDH-dependent RA signaling is involved in gene expression and morphogenesis and is crucial for normal

development (*Figure 2*) (6,12-14).

In a recent study which is the focus of this perspective, Cojoc *et al*. (15) examined the regulation of ALDH in prostate cancer stem cells (PCSCs) and its role in prostate tumor radioresistance. One of the major factors contributing to prostate cancer patient mortality is relapse following radiotherapy (16); therefore, it is crucial to identify the mechanisms that surviving cells, presumably CSCs, utilize to evade this lethal treatment and reestablish the tumor. The primary translational goal of this study was to evaluate ALDH activity as an effective prognostic biomarker for prostate cancer curability. Prostate cancer is the second most common cancer in American men with approximately 15% diagnosed during their lifetime (17). More than 26,000 American men die each year, and the majority of those from recurrent or metastatic disease. Thus, it is important to diagnose those at higher risk for secondary tumors and develop new treatments to combat this problem. Despite CSCs typically being lumped together as one entity, there are many variables among CSCs, even from the same tumor type, that can alter efficacy of radiotherapy as well as chemotherapeutic treatments (18). Currently, PCSCs are typically characterized by CD44+, CD133+, integrin α2β1+, ALDHhi cells (19,20). Identifying a single prognostic marker for PCSCs, such as ALDH activity, would aid in clinical evaluation.

ALDH proteins and general activity have been implicated in radiation resistance and tumor recurrence in several cancers including breast and esophageal (21,22). In order to identify genes expressed in tumor PCSCs, these cells were enriched for and isolated from a mouse xenograft tumor and genome expression analyzed (15). These cells showed a correlation between CD44+/CD133+ PCSCs and levels of ALDH1A1, ALDH3A1, ALDH3B1, and ALDH6A1; with ALDH1A1 and ALDH6A1 also being significantly enriched in prostate carcinomas compared to normal prostate tissue. Consistent with previous reports (20,23), ALDH+ cells had increased capacity to form spheres and colonies and had significantly greater frequency of tumor-initiating cells. ALDH+ cells were capable of regenerating prostate cancer tumor cell types in culture and in mouse xenograft. This confirms and expands upon the findings from earlier studies indicating that ALDH activity and expression of ALDH1A1 both correlate with tumor stage and patient survival and tumorigenicity and metastasis in animal models (24,25). Together this indicates that ALDH, or at least ALDH1A1, may be useful as a marker for PCSCs.

In order to examine the relation between ALDH and irradiation, prostate cancer cell lines and primary prostate tumor cells were exposed to varying doses of X-rays (15). There was a dose-dependent increase in ALDH activity and expression of CSC markers and β-catenin in the cancer cells but not in normal, immortalized prostate epithelial cell line (RWPE-1). This is consistent with previous studies showing irradiation triggers enrichment of CSC populations (22,26). Interestingly, prostate cells selected for enhanced radioresistance maintained greater ALDH activity and stem cell marker expression, and exhibited a higher baseline activation of DNA damage response (DDR) as indicated by phosphorylation of kinases AKT (Ser 473) and CHK2 (Thr 68). These proteins activate other DDR proteins and are essential for proper regulation of the DNA damage checkpoint (27). The high basal activation of CHK2 correlated with ALDH activity in radioresistant prostate cancer cells. Upon irradiation these cells had fewer γH2AX foci after one hour and 24 hours, indicating that there were both less DNA double strand breaks formed and more efficient repair of breaks. We previously found that depleting ALDH1A1 caused decreased phosphorylation/activation of CHK1 (Ser 317), PARP and Fanconi Anemia DNA repair pathway proteins and increased γH2AX levels (28) in response to carboplatin treatment in ovarian cancer cells lines. Loss of ALDH1A1 also disrupted the cell cycle profile of ovarian cancer cells. These findings indicate that ALDH1A1 enhances activation of DNA strand break resistance and repair, suggesting an important role for this protein in resistance to DNA damage induced by X-ray irradiation and certain chemotherapeutic drugs.

It appears, however, that enhanced DNA repair may only be part of the story. Radioresistant prostate cancer cells had lower baseline ROS, and ALDH+-derived xenograft tumor cells had high ALDH1A1 levels and low ROS production (15). ROS production is stimulated by irradiation and causes DNA damage (29-31). Interestingly, ROS-induced DNA damage has been implicated in gene regulation (32,33); thus it would be interesting to determine how ALDHs affect transcription of genes regulated in this manner. CSCs also appear to be protected from radiation-induced DNA damage by residing in a hypoxic niche inside prostate tumors, as ALDH1A1 and HIF1α expression correlated (15). The combination of protective niche, increased DNA repair and decreased ROS levels would be effective to protect ALDH+ PCSCs from the effects of anti-tumor radiotherapy.

Multiple WNT proteins and the pathway effector transcription factor, β-catenin, were found to be upregulated

in irradiated prostate cancer cells (15). The WNT signaling pathway has been implicated in carcinogenesis and in maintenance of CSCs in many cancers and correlates with epithelial mesenchymal transition (EMT), metastasis and resistance to treatment (34-36). Furthermore, CSCs that survive radiation treatment display characteristics of EMT (37-40). The current study found that ALDH+ cells had both higher levels of β-catenin and a higher percentage in the nucleus where it functions, than were seen in ALDH- cells (15). To determine if the WNT pathway regulates expression of ALDHs, cells were treated with the tankyrase inhibitor XAV939 which stimulates degradation of β-catenin or siRNA targeting β-catenin. Inhibiting the WNT pathway diminished ALDH+ population and induced radiosensitization in multiple prostate cancer cell lines. There was also a concomitant loss of ALDH1A1 expression, and examination of the *ALDH1A1* promoter region yielded two consensus β-catenin/TCF recognition sites. Chromatin immunoprecipitation analysis found that the β-catenin/TCF transcriptional complex binds the ALDH1A1 promoter and a luciferase reporter assay indicated β-catenin directly promotes expression from the ALDH1A1 promoter. This is an important finding as WNT/β-catenin is considered a high potential target for chemotherapy (41,42). Another regulatory pathway controlling expression of ALDH1A1 was recently elucidated by Alam *et al*. They found that in breast cancer cells the oncogenic MUC1-C induces the extracellular signal-regulated kinase (ERK) signaling pathway leading to phosphorylation and activation of the transcriptional regulator C/EBPβ (43). A complex of MUC1-C and C/EBPβ then binds to the *ALDH1A1* promoter and promotes expression. This indicates that there are multiple regulatory mechanisms promoting expression of ALDH1A1 in cancer cells making it difficult to target its expression as a cancer treatment.

The findings of this study indicate that the WNT signaling pathway regulates ALDH1A1 expression and that ALDH activity promotes a CSC phenotype and resistance to radiation through enhanced DNA repair and decreased ROS (15). PCSCs with high ALDH activity are very tumorigenic and can reproduce multiple tumor cell types, suggesting that these cells are likely to evade radiotherapy and promote tumor recurrence. The evidence presented strongly suggests that ALDH is a likely prognostic indicator for efficacy of radiation treatment and susceptibility for prostate cancer recurrence and should be thoroughly examined in clinical trials. This is consistent with studies indicating that ALDH activity or expression of one or more ALDH protein correlate with tumor aggressiveness, treatment resistance, metastasis, and poor patient prognosis (6,25,44). ALDH has been proposed as a prognostic marker for many cancers including lung (45), breast (46), ovarian (47), pancreatic (24), and colon (48). There are many excellent recent reviews of ALDHs in cancer and CSCs (6,49-52) and these topics will not be discussed in detail here. ALDH has been most extensively studied in breast cancer where it correlates with tumor grade, ER negativity, HER2 positivity and poor patient survival (44,53,54). ALDH1+ breast cancer cells are at least 100 fold more tumorigenic than ALDH- cells in mice (44). Curiously, unlike most other tumors studied, in melanoma, high ALDH activity actually correlates with good patient prognosis (55). ALDHs have been proposed as a universal marker for identification for both normal stem cells as well as CSCs (6). And ALDH activity is commonly utilized to enrich stem cell populations from tumors, cell lines and normal tissues (24,56).

While ALDH appears to be an effective prognostic marker for many tumors, the important question remains: is ALDH a good therapeutic target for eliminating CSCs and preventing tumor recurrence? This remains a controversial subject for several reasons. Firstly, many of the studies examining the roles of ALDHs failed to identify specific proteins involved. There are 19 different ALDHs and most studies have not examined the roles of individual proteins. This is due to a lack of specific antibodies to differentiate the ALDHs and the ease and widespread use of the ALDEFLUOR assay, a simple and rapid technique to monitor and isolate cells by ALDH activity using FACS. Multiple ALDH isoforms can oxidize the substrate used in this assay and therefore, it is impossible to determine which enzymes are contributing to measured activity, and many ALDHs are not measured by this method (57). Therefore, more detailed, in depth analysis needs to be conducted to determine which ALDHs are the primary contributors to stemness, treatment resistance, tumor proliferation and aggression and metastasis; which may be tumor type or even patient specific. There is also evidence suggesting significant overlap between ALDHs and thus inhibiting one could result in others compensating for its activity (58). Furthermore, ALDHs are widely distributed throughout the body, have vital functions, and are highly expressed in certain normal organ tissues such as the liver and kidney (6,50) making it more difficult to specifically target tumors.

Recently, Hurley has had some early success designing specific small molecule inhibitors for ALDH1A1, ALDH2,

and ALDH3A1 (59), indicating that this strategy is possible. ALDH1A1 has been frequently identified as being clinically relevant and as a potential chemotherapeutic target (6). Inhibiting ALDH1 has been shown to sensitize ALDHhi breast cells to paclitaxel and epirubicin (22) indicating it is a plausible target. Interestingly, ALDH1A1 promotes expression of the kinase NEK2, which directly increases the activity of multidrug efflux pumps (3). These proteins are expressed at high levels in CSCs and protect cells by removal of xenobiotic compounds, including many chemotherapeutic agents and serve as a primary cause of chemoresistance in CSCs (60). This further complicates targeting ALDH1A1 as many drugs may be ineffective because they cannot reach their intended target.

One particularly intriguing way to target ALDHs involves treatment with vitamin A-related compounds, known as retinoids. RA signaling is derived from vitamin A (retinol), crucial for embryogenesis and development (61) and functions in cellular proliferation, differentiation, and apoptosis and survival (6,49,51). ALDHs convert retinaldehyde to RA. RA is the signaling effector molecule and binds retinoic acid receptors (RAR) or retinoid X receptors (RXR) (62), which then bind specific DNA sequences in promoters to regulate gene expression (13,63). Several retinoids have previously been investigated for treating cancers to increase effectiveness of standard chemotherapy (64-66). These drugs activate RA signaling which decreases expression of stemness markers promoting cellular differentiation, promotes cell cycle arrest and decreases cellular proliferation and reduces tumor growth in mice (67).

All-trans retinoic acid (ATRA) is an RA signaling molecule that has been extensively tested as a therapeutic agent. It decreases ALDH1A1 and ALDH3A1 activity and drives differentiation of CSCs (68). ATRA was approved by the United States Food and Drug Administration for acute promyelocytic leukemia (APL) in 1995 (69). Combining ATRA with standard chemotherapy has led to a greater than 90% remission rate for AML (70) and is considered a major success story. Sadly, studies using ATRA and other RA compounds for various tumors have thus far yielded mixed results (49), likely due to high incidence of acquired retinoid resistance seen in many solid tumors. However, the limited success achieved using RAs in combination with other chemotherapeutic drugs is sufficient to warrant further studies.

There have been a few studies suggesting that certain dietary compounds are capable of targeting ALDH+ tumors and CSCs. Circumin and piperine are natural chemicals produced in plants and can be found in various foods including turmeric and black pepper, respectively. Treating breast cancer cells with these compounds led to a decrease in the percentage of ALDH+ cells and impaired mammosphere formation (a measure of stemness in breast cancer cells) (71). Sulforaphane is an isothiocyanate (ITC) compound found in many cruciferous vegetable, such as broccoli, cabbage and Brussels sprouts that also acts to reduce numbers of ALDH+ cells and mammosphere formation and slow tumor growth in breast cancer (72). These three compounds have been extensively tested and are still actively being examined as anticancer agents and have some potential for clinical applications (73).

While current cancer treatment strategies, including surgical resection, chemotherapy and radiation are quite effective at eliminating the primary tumor, many patients experience disease relapse or metastasis. It is these secondary tumors which are now responsible for the majority of cancer deaths in the United States. CSCs are typically highly resistant to anticancer treatments and are thought to be responsible for most cases of tumor recurrence and metastasis. It is significant that several recent studies have found that treating cancer cells with X-rays or chemotherapeutic agents can actually increase the expression of stem cell markers and associated stemness characteristics in surviving cells (22,26,74,75). This strongly indicates that CSCs are a roadblock to successful tumor resolution and a major threat to patient survival. To this end, there is currently a great deal of work investigating new drugs that can kill CSCs or trigger their differentiation into normal tumor cells which can then be targeted by conventional treatments (*Figure 1*). ALDHs are a family of proteins that are highly expressed in both normal stem cells and CSCs and important for regulating differentiation of these cells, making them intriguing targets. ALDHs appear to have great value as prognostic indicators for tumor aggressiveness, resistance and survival. While there have been some preliminary success using drugs that regulate ALDHs or retinoic acid signaling, much work remains to be done to develop effective chemotherapeutic drugs to improve patient survival. Variations in different ALDHs, tissues, tumors and other conditions will have to be addressed in order to maximize the efficiency of drugs targeting these proteins of the RA signaling pathway in which they function. The excellent studies by Cojoc *et al*. (15) discussed here and others bring clarity to a complex and murky field and may

someday benefit many cancer patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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