

Cancer Stem Cell Antigen's Increasing Role in Leukemia and other diseases

Abstract

Aldehyde dehydrogenase 1A3 (ALDH1A3) is one of 19 ALDH enzymes expressed in humans and is important for the production of the hormone receptor ligand retinoic acid (RA). We are investigating her role of ALDH1A3 in normal physiology, its identification as a marker for cancer stem cells, and its mechanism of action in cancer and other diseases. ALDH1A3, which is often overexpressed in cancer, promotes tumor growth, metastasis, and chemoresistance by altering gene expression, cell signaling pathways, and glucose metabolism. Elevated ALDH1A3 levels in cancer are caused by gene amplification, epigenetic modifications, post-transcriptional regulation and post-translational modifications. Finally, we confirm the potential to target ALDH1A3 using both general ALDH inhibitors and small molecules specifically designed to inhibit ALDH1A3 activity.

Keywords: cancer stem cells • Cell signaling • Gene expression • Diabetes • Inhibitors

Introduction

In 2011, a then little-studied cancer-associated enzyme, aldehyde dehydrogenase 1A3 (ALDH1A3), was shown to produce high aldehyde activity associated with breast cancer stem cells (CSCs) [1]. Since then, his interest in studying the role of ALDH1A3 in cancer and the possibility of targeting ALDH1A3 has grown exponentially. In addition, ALDH1A3 plays an important role in other diseases, such as the development of type 2 diabetes, in which dysregulation of her ALDH1A3 in pancreatic β -cells impairs insulin production. This review provides a broad overview of the function of ALDH1A3 in both normal and disease settings [2]. We describe its expanding mechanism of action and mechanisms of ALDH1A3 regulation in cancer. Finally, the development of increasingly specific ALDH1A3 inhibitors suggests an increasing potential for clinical targeting of ALDH1A3 [3].

Is a member of the ALDH

ALDH1A3 is generally expressed at low levels in the body and at high levels in salivary glands, stomach and kidney. ALDH1A3 is his sixth ALDH enzyme discovered in the human genome, and he was originally named ALDH6. Ultimately, 19 of her ALDH enzymes, expressed from different loci of the human genome, would be discovered [4]. Nineteen members make up her ALDH superfamily and share at least 40% sequence homology, with subfamily members sharing at least 60% homology. ALDH catalyzes the irreversible oxidation of aldehydes to carboxylic acids by binding the aldehydes to the cofactor nicotinamide adenine dinucleotide (NAD⁺) or NAD phosphate (NADP⁺). In general, ALDH helps remove toxic aldehydes produced during metabolic processes, including endogenous aldehydes resulting from lipid peroxidation, amino acid catabolism, and exogenous xenobiotics. In addition, isoforms have different expression profiles in somatic tissues, different subcellular localizations (cytoplasm, nucleus, endoplasmic reticulum or mitochondria), substrate specificities and functions. Of relevance to this review is that the homologous ALDH1A1, ALDH1A2, and ALDH1A3 isoforms share 70% amino acid sequence homology, are present in the cytoplasm, and are mediated by the vitamin A metabolites all-trans-retinal to all-trans-retinoic acid (ATRA), generally retinoic acid) oxidizing acid, RA) [5]. Because of this retinal oxidative activity, ALDH1A1, ALDH1A2, and ALDH1A3 are also called retinal dehydrogenase 1 (RALDH1), RALDH2, and RALDH3, respectively [6].

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ALDH1A3 is expressed in the ventral retina and its loss causes anophthalmia and abnormal eye development in humans and animal models. ALDH1A3 knockout in mice is neonatal lethal, with severe defects in nose and eye development due to RA deficiency during critical developmental stages. A comparative analysis of the three her ALDH1A enzymes revealed similar structural topologies, with ALDH1A3 having the smallest substrate-binding pocket. ALDH1A3 had the highest enzymatic activity in converting all-trans-retinal to RA, followed by he was ALDH1A2, although it had the lowest activity compared to the other substrates tested. This was consistent with previous reports suggesting a higher capacity for her RA biosynthesis for her ALDH1A3 than for ALDH1A1 [7].

Retinoic Acid is key function enzyme

It is a ligand for the nuclear hormone receptor retinoic acid receptor (RAR) that can modulate the expression of hundreds of genes and produce a variety of cellular effects. A prerequisite for RA signaling is that cells are able to metabolize vitamin A (retinol) to retinal and then from retinal to RA [8].

RA binds to the nuclear hormone receptor retinoic acid (RAR) α , β , and γ , which heterodimerize with the retinoid X receptor (RXR). Heterodimers regulate gene expression by binding to retinoic acid receptor element (RARE) sequence motifs found in the promoter and enhancer regions of over 3000 genes in the genome. Binding of RA to these heterodimeric nuclear hormone receptors can have both activating and repressing gene expression effects. Gene induction is observed when binding of RA to RAR promotes binding of nuclear receptor coactivators and other coactivators such as histone acetylases (HATs) [9]. Conversely, in a less understood mechanism, gene repression by RA involves RA-mediated polycomb repressive complex 2 (PRC2) and nuclear hormone receptor heterodimers of the superfamily histone deacetylases (HDACs). involves mobilization to RA signaling in the physiological range (nM level) is mediated by the ALDH1A enzyme and has effects distinct from the supraphysiological effects induced by pharmacological RA treatments in the μM range [10]. Supraphysiological amounts of RA can inhibit cell proliferation

and induce cell death and differentiation, as has been observed in the treatment of acute promyelocytic leukemia. In contrast, retinoid and vitamin A deficiencies exacerbate the condition. Gene expression analysis showed increased expression of her ALDH1A3 in patients with asthma, whereas another study found no change in her ALDH1A3 protein expression levels [11].

Taken together, these studies suggest that in the context of cancer and other diseases, the pharmacological effects of retinoid treatment are often distinct from physiologic RA signaling through ALDH1A, and the two do not necessarily equate.

Cancer in Prognosis

Consistent with the association of ALDH1A3 with CSCs, ALDH1A3 expression in cancer is commonly associated with poor prognosis, disease progression, and recurrence [12]. In breast cancer, patients' tumors with high levels of her ALDH1A3 were associated with an increased incidence of metastasis compared with patients with low levels of triple-negative breast cancer (TNBC), a more aggressive subtype of breast cancer. was doing. In TNBC, ALDH1A3 is associated with decreased survival. Moreover, high expression of ALDH1A3 is associated with poor patient survival in prostate, glioblastoma, neuroblastoma, pancreatic, gastric, gallbladder, colon, and intrahepatic cholangiocarcinomas [13]. High ALDH1A3 levels correlate with increased tumor grade in breast, glioblastoma, bladder, and prostate cancers. Bladder, breast, and intrahepatic cholangiocarcinomas have been shown to have elevated ALDH1A3 expression with higher tumor stage.

ALDH1A3 is associated with increased tumor progression and poor prognosis in many types of cancer, but increased ALDH1A3 expression is associated with increased tumor progression in TP53 wild-type ovarian tumors, BRAF-mutant metastatic melanoma, and non-small cell lung cancer [14]. It is also associated with improved outcomes. These positive clinical correlations with ALDH1A3 in different contexts suggest that the effects of ALDH1A3 in cancer may be specific to the cellular context and dependent on the presence of other molecular factors.

Although the increased metastasis associated

with elevated ALDH1A3 may be an indirect result of increased tumor burden and cancer cell proliferation, there is also evidence that ALDH1A3 directly increases the metastatic potential of cancer cells. Although there are many reports of ALDH1A3 affecting invasion and/or migration, these effects appear to be cancer type dependent. In breast cancer, elevated ALDH1A3 increases transwell invasion of TNBC MDA-MB-231 cells. The increased invasive/metastatic potential conferred on breast cancer cells by ALDH1A3 appears to be associated with decreased migration. Her ALDH1A3 knockdown in TNBC MDA-MB-468 and SUM159 cells increased adhesion and migration while decreasing metastasis in the chicken chorioallantoic membrane assay. ALDH1A3 knockdown in cholangiocarcinoma cell lines reduces migration. Reports also suggest that ALDH1A3 confers increased colony formation, or clonogenicity. It measures the ability of single cells to form colonies and is an in vitro indicator of tumor-initiating capacity required for the formation of primary and secondary tumors. In a panel of lung cancer cell lines, ALDH1A3 knockdown reduced colony formation in 11 of 12 cell lines. In breast cancer, ALDH1A3 mediated increased colony formation in TNBC MDA-MB-231 and MDA-MB-468 cells. Similarly, reduction of ALDH1A3 resulted in decreased colonization in colon and gastric cancers.

In summary, ALDH1A3 may promote tumor progression through effects on proliferation, apoptosis, migration, invasion and clonogenicity. Growing evidence that ALDH1A3 is a key factor in cancer progression in multiple types of cancer suggests that ALDH1A3 is a promising therapeutic target. Recent advances in targeting ALDH1A3 are discussed later in this review [15].

Regulation in Cancer

ALDH1A3 upregulation in cancer occurs through multiple mechanisms. As explained in the Role of His ALDH1A3 in Multidrug Resistance section above, transcriptional upregulation of His ALDH1A3 in cancer involves epigenetic histone modifications of its promoter. or indirect upregulation by STAT3-NF- κ B and activation of the transcription factor CEBP β . Similarly, in mesenchymal glioma stem cells, the transcription factor Foxhead box D1 (FOXD1)

regulates the expression of her ALDH1A3, and the FOXD1-ALDH1A3 axis contributes to the self-renewal and tumorigenic properties of glioma stem cells. It is important. In glioma stem cells, ALDH1A3 levels are also dysregulated at the protein level and ubiquitin-specific protease 9X (USP9X) deubiquitinates his ALDH1A3, leading to stabilization and elevation of levels. In addition to the epigenetic regulation by histone modifications described above, DNA methylation of the ALDH1A3 promoter causes downregulation of ALDH1A3 in glioblastoma. In these two studies, ALDH1A3 hypermethylation was associated with better prognostic outcome, consistent with a cancer-promoting role of ALDH1A3. In contrast, in bladder cancer, ALDH1A3 hypermethylation was associated with disease progression and recurrence in non-muscle-invasive bladder cancer. ALDH1A3 produces RA, the ligand for the nuclear hormone RAR-RXR heterodimer, leading to transcriptional regulation of genes by RAREs, as described in the section "Retinoic Acid Signaling - A Key Function of the ALDH1A Enzyme". A pan-RAR antagonist inhibited the expression of ALDH1A3. In colorectal cancer cells, ALDH1A3 expression is induced through the Hippo signaling pathway activator Yap via RAR-RXR transcriptional coactivator activity. ALDH1A3 is frequently regulated by post-transcriptional regulation by noncoding RNAs, both long noncoding RNAs (lncRNAs) and microRNAs (miRNAs). Scaffolding, protein and RNA binding. In contrast, miRNAs that are 18–25 nucleotides in length negatively regulate the stability and translation of their target mRNAs.

Conclusions

This review provided the most comprehensive and up-to-date overview of ALDH1A3. The role of his ALDH1A3 as a CSC marker is well established. Generalizations that emerge from our ALDH1A3 literature review suggest that it has tumor growth and metastatic effects in cancer. Mechanistic studies suggest that ALDH1A3-mediated cancer progression and general chemoresistance are due to ALDH1A3-mediated gene expression effects. ALDH1A3-induced changes in gene expression were often associated with RA signaling. However, there are recent studies describing miRNA- or lncRNA-

mediated regulation of gene expression. Not surprisingly, given its diverse functional roles, ALDH1A3 has been implicated in multiple cancer types and has prognostic relevance. Since ALDH1A3 is a metabolic enzyme, the association of ALDH1A3 with metabolic diseases such as diabetes is predictable, and there is growing evidence of its impact on glucose metabolism.

Evidence suggests that ALDH1A3 may be a new therapeutic target for various diseases, and we have detailed previously reported inhibitors of ALDH1A3. Although ALDH1A3 inhibitors have not yet been evaluated in clinical trials, this seems likely in the future as inhibitors in development have increased specificity and demonstrated preclinical efficacy.

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