Advances in World Medical Research, 2025, 1(2), 1-14
https://doi.org/10.71204/50ww5z23

Study on the Role and Related Mechanism of ALDH1B1 in the Development of Colorectal Cancer

Chi Gao [1], Jianwei Qiao [1], Weijie Li [1], Zhihui Tai [1,*]

[1] Affiliated Hospital of North China University of Science and Technology, Tangshan 063000, China

*** Correspondence**:

Zhihui Tai

keepw@126.com

Received: 6 June 2025/ Accepted: 17 August 2025/ Published online: 20 August 2025

Abstract

Aldehyde dehydrogenases (ALDHs) comprise a broad superfamily of metabolic enzymes, with 19 gene groups identified in the human genome. These genes participate in diverse biological processes, including the detoxification of exogenous and endogenous aldehydes. In recent years, ALDHs have garnered increasing attention due to their association with stem cell-related characteristics in a wide range of hematopoietic malignancies and solid tumors. ALDH1B1, an isoform and member of the ALDH superfamily, is aberrantly expressed in multiple cancers. For instance, ALDH1B1 is dysregulated in pancreatic cancer (particularly pancreatic ductal adenocarcinoma, PDAC), where it drives tumor progression through multiple mechanisms: maintaining stemness (e.g., activating Notch and Wnt/ β -catenin pathways), metabolic reprogramming (acetaldehyde metabolism, reducing toxic aldehyde accumulation while generating NADPH to sustain redox balance), activating oncogenic pathways (e.g., inducing WNT signaling to promote epithelial-mesenchymal transition and enhance invasiveness), and conferring therapy resistance. ALDH1B1 overexpression induces significant changes in cell morphology, proliferation rates, and clonogenic efficiency, thereby contributing to lung adenocarcinoma development. In esophageal carcinogenesis, three genome-wide significant loci in heterozygotes include ALDH1B1, which exhibits a genome-wide significant interaction with rs671, potentially increasing the risk of esophageal cancer (a classic alcohol-associated disease). Domestic studies have shown that miR-761 can target and suppress ALDH1B1 to inhibit osteosarcoma cell proliferation, migration, and invasion. Furthermore, ALDH1B1 promotes colorectal cancer progression by regulating cancer stemness and key oncogenic signaling pathways. This article elucidates the mechanistic roles of ALDH1B1 in various malignancies, with a particular focus on its specific interactions in the development and progression of colorectal cancer. Notably, ALDH1B1 promotes colorectal carcinogenesis by mediating unique metabolic reprogramming processes. On one hand, ALDH1B1 maintains intracellular redox balance through acetaldehyde oxidation, creating a favorable metabolic microenvironment for

cancer stem cells. On the other hand, its involvement in retinoic acid metabolism dysregulation aberrantly activates key oncogenic pathways such as Wnt/β-catenin signaling. Furthermore, ALDH1B1 enhances the glycolytic switch (the Warburg effect) by modulating mitochondrial energy metabolism, thereby supplying the bioenergetic and biosynthetic precursors required for rapid tumor cell proliferation. These metabolic regulatory mechanisms synergize with ALDH1B1′s role in sustaining cancer stem cell properties, collectively forming a multidimensional network through which ALDH1B1 drives colorectal cancer progression. A deeper understanding of the logical relationship between ALDH1B1-mediated metabolic regulation and carcinogenesis will provide a more comprehensive insight into its role in various cancers, particularly colorectal cancer, and offer a theoretical foundation for developing novel ALDH1B1-targeted therapeutic strategies. However, more detailed molecular mechanisms, clinical relevance, and potential therapeutic value require further experimental and clinical validation.

Keywords: ALDH1B1; Cancer Stem Cells; Wnt/β - Catenin; Notch Signaling Pathways; Metabolic Reprogramming; Malignant Tumors; Colorectal Cancer

1. Introduction

1.1. The Structure of ALDHs

Aldehyde dehydrogenases (ALDHs) represent a crucial class of metabolic enzymes that catalyze the NAD(P)+dependent oxidation of various aldehydes to their corresponding carboxylic acids, utilizing either nicotinamide adenine dinucleotide (NAD+ or its phosphorylated form (NADP+) as essential cofactors (Muzio et al., 2012). Structurally, these enzymes feature distinct functional regions including specialized NAD(P)+binding sites for cofactor interaction and catalytic sites that drive the oxidation process. As members of an extensive enzyme superfamily, ALDHs encompass 19 known isoforms that share four characteristic structural domains critical for their function. The catalytic domain stands out with its highly conserved glutamate active site (particularly Glu268 in ALDH1B1), which facilitates both substrate binding and the oxidation reaction, complemented by an NAD(P)+binding motif essential for dehydrogenase activity. Protein oligomerization occurs through a dedicated domain that promotes the formation of functional dimers or tetramers via specific helix-helix interactions, while substrate specificity is governed by a unique channel domain composed of β-sheets and α-helices that creates a hydrophobic pathway for selective aldehyde recognition. Additional conserved features include catalytic cysteine residues (notably Cys302) and characteristic NAD(P)+binding sequence patterns. Of particular clinical significance, multiple ALDH isoforms - including ALDH1A1, ALDH1A3, ALDH3A1, ALDH5A1, ALDH7A1, and ALDH18A1 - have been identified as molecular markers associated with cancer stem cells (CSCs) (Lavudi et al., 2024). While these enzymes naturally occur in CSCs, their unique expression patterns have proven invaluable for the identification and isolation of tumorigenic cell populations exhibiting stem-like properties across various cancer types (Toledo-Guzmán et al., 2019).

1.2. The Structure of ALDH1B1

Aldehyde dehydrogenase 1 family member B1 (ALDH1B1) is a protein-coding gene located on chromosome 9p13.1 that encodes a mitochondrial-localized enzyme. The gene contains a 1,503 bp open reading frame that translates into a 508-amino acid protein with an approximate molecular weight of 56 kDa (source: GeneCards). Characteristically, ALDH1B1 features an N-terminal adenylate binding site (NAD+binding site) and belongs to the aldehyde dehydrogenase superfamily, containing three highly conserved functional domains: the NAD+binding domain responsible for cofactor NAD(P)+ binding; the catalytic domain containing a conserved cysteine residue (Cys302) that acts as a nucleophile in aldehyde oxidation; and the oligomerization domain mediating tetramer formation. This multifunctional enzyme demonstrates detoxification capabilities toward lipid peroxidation byproducts including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), while also metabolizing nitroglycerin and all-trans-retinal (Tsochantaridis et al., 2021). Additionally, ALDH1B1 contains a catalytic site at its C-terminus, which is responsible for carrying out aldehyde dehydrogenase reactions. In cells, this enzyme mainly takes part in redox reactions and shows strong aldehyde dehydrogenase activity. Because of this function, it plays a key role in breaking down harmful aldehydes and maintaining cellular balance. Additionally, ALDH1B1 helps convert aldehydes into less toxic acids, supporting important metabolic processes. Its activity is crucial for protecting cells from oxidative stress and ensuring proper metabolic function.

2. Structure, Function of ALDH1B1 and Its Role in Malignant Tumors

2.1. The Biological Function of ALDH1B1

2.1.1. Metabolic Regulation and Cancer Development

ALDH1B1, a mitochondrial aldehyde dehydrogenase, plays crucial roles in oxidizing short-/medium-chain aliphatic aldehydes, retinaldehyde, and lipid peroxidation byproducts. Through mitochondrial metabolic regulation, its deficiency or inhibition alters the expression of mitochondrial metabolism-related genes, potentially affecting cancer cell survival by disrupting energy metabolism. Emerging evidence demonstrates that ALDH1B1 is overexpressed in colorectal and pancreatic cancers, where it promotes tumorigenesis via metabolic reprogramming. Notably, selective ALDH1B1 inhibitors significantly suppress colorectal cancer cell proliferation, highlighting its potential as an anticancer therapeutic target (Feng et al., 2022; Wood et al., 2016). Furthermore, ALDH1B1 contributes to cellular homeostasis by detoxifying toxic aldehydes such as 4-hydroxynonenal (4-HNE). Mechanistically, eukaryotic translation initiation factor 4E (EIF4E) interacts with ALDH1B1 in mitochondria through a mitochondrial targeting signal dependent on Ser53 phosphorylation, thereby regulating local 4-HNE metabolic balance. Intriguingly, ferroptosis inducers (e.g., RSL3) promote the formation of EIF4E-ALDH1B1 complexes via iron-dependent pathways, subsequently inhibiting ALDH1B1 function. This inhibition leads to 4-HNE accumulation, ultimately modulating oxidative stress responses and cellular sensitivity to ferroptosis (Chen et al., 2022).

2.1.2. DNA Damage Response（DDR）

ALDH1B1 is functionally implicated in DNA damage repair (DDR) processes. In colorectal adenocarcinoma, ALDH1B1 expression levels directly modulate cellular sensitivity to DNA-damaging agents. Mechanistic studies reveal that ALDH1B1 overexpression correlates with translational upregulation of p53 protein and its phosphorylation at Ser15 in colorectal adenocarcinoma cells, suggesting its involvement in cell cycle regulation (particularly G2/M phase arrest) and DDR activation through the p53 pathway. This is further supported by observed increases in constitutive phosphorylation levels of H2AX at Ser139 (γH2AX)(Tsochantaridis et al., 2022).Further evidence shows that ALDH1B1 plays a role in the DNA damage response (DDR) by promoting the formation of γH2AX, a well-known marker of DNA damage. When DNA is damaged, cells produce γH2AX as a signal to start the repair process. Since ALDH1B1 helps increase γH2AX levels, this suggests it is actively involved in DDR. This function may be important for maintaining genomic stability and preventing harmful mutations. Therefore, ALDH1B1 likely contributes to cellular defense mechanisms by supporting DNA damage recognition and repair.

2.1.3. Antiviral Immune Regulation

Recent studies have identified ALDH1B1 as an interferon-stimulated gene (ISG) product that suppresses replication of diverse RNA viruses by enhancing type I interferon (IFN-β) production. Mechanistically, ALDH1B1 directly binds to the transmembrane domain of mitochondrial antiviral-signaling protein (MAVS), promoting the formation of prion-like functional aggregates. These aggregates serve as critical platforms for RIG-I-like receptor (RLR) signalosome activation, particularly facilitating RIG-I-mediated downstream antiviral signaling. ALDH1B1 potentiates antiviral responses by strengthening the interaction between activated RIG-I and MAVS, thereby amplifying MAVS-mediated signaling cascades. This enhancement leads to significantly increased IFN-β secretion and robust antiviral activity against pathogenic RNA viruses including Zika and Dengue viruses(Sun et al., 2024). Consequently, ALDH1B1 deficiency compromises host antiviral defense mechanisms, demonstrating its essential role in innate immunity.

2.1.4. The Relationship Between Alcohol Metabolism and Diabetes

ALDH1B1 plays a pivotal role in ethanol metabolism as a mitochondrial aldehyde dehydrogenase family member, exhibiting high efficiency in oxidizing acetaldehyde (second only to ALDH2). Genetic knockout (KO) mouse models demonstrate that ALDH1B1 deficiency elevates blood acetaldehyde levels by approximately 40%, confirming its essential function in systemic acetaldehyde clearance. Notably, ALDH1B1 polymorphisms correlate with alcohol sensitivity, particularly when variant isoforms exhibit reduced acetaldehyde metabolic rates, potentially influencing susceptibility to alcohol-related disorders. Phenotypic characterization of ALDH1B1 KO mice reveals significantly elevated fasting blood glucose levels (+60%) despite normal glucose tolerance test (GTT) results, suggesting its involvement in basal glucose regulation through indirect mechanisms such as insulin/glucagon secretion or hepatic glucose metabolism. Developmental studies highlight ALDH1B1's abundant expression in pancreatic progenitor cells during embryogenesis and in regenerating cells following pancreatic injury in

adults, implicating its role in maintaining pancreatic functional integrity and glucose homeostasis(Singh, Chen, et al., 2015).Collectively, these findings establish ALDH1B1 as a crucial metabolic regulator at the intersection of alcohol metabolism and diabetes pathogenesis, with additional implications for stem cell function and tumorigenesis. This research provides novel insights into the mechanistic links between alcohol-related diseases, diabetes, and cancer development.

2.1.5. Cell Necrosis and Liver Diseases

ALDH1B1 serves as a critical regulator of reactive oxygen species (ROS) homeostasis. In NR5A2-deficient hepatocytes, downregulation of ALDH1B1 expression leads to markedly elevated ROS levels, subsequently activating pro-inflammatory signaling pathways. Mechanistically, ALDH1B1 suppresses NF-κB pathway activation through ROS scavenging - while ROS accumulation typically stimulates NF-κB inflammatory signaling, ALDH1B1 indirectly inhibits NF-κB phosphorylation by eliminating ROS. This is evidenced by reduced nuclear translocation of NF-κB-p65 and decreased expression of downstream inflammatory mediators (including NLRP3 and IL-1β) in ALDH1B1-overexpressing cells. Importantly, NR5A2 deficiency-induced ALDH1B1 downregulation triggers ROS accumulation, which activates the NF-κB-NLRP3 axis and subsequently promotes Caspase-1/GSDMD-mediated pyroptosis. ALDH1B1 overexpression reverses this pathological cascade, attenuating cell membrane rupture and inflammatory cytokine release (e.g., LDH and IL-1β)(Zhao et al., 2024). These findings establish that ALDH1B1, under transcriptional control of NR5A2, exerts both antioxidant and anti-inflammatory effects by inhibiting the ROS-NF-κB-pyroptosis axis, thereby protecting hepatocytes from NASH-associated damage. This mechanistic insight identifies ALDH1B1 and NR5A2 signaling as potential therapeutic targets for NASH intervention.

2.2. Relevance Between ALDH1B1 and the Development of Others Malignant Tumor

Research has explored the potential prognostic and diagnostic roles of ALDHs, with studies demonstrating that ALDH1A3 expression affects breast cancer patient survival via retinoic acid (RA) signaling(Marcato et al., 2015), ALDH2 regulates lung cancer development(Tran et al., 2023), differential expression of ALDH family genes across ethnicities influences hepatocellular carcinoma progression and prognosis (Yao et al., 2022)and ALDH-1 has prognostic implications in esophageal cancer (Hwang et al., 2014). These findings collectively highlight the diverse roles of different ALDH family members in the initiation and progression of various tumors.

ALDH1A3 increases the number of ALDHs by altering CD24 and CD44 transcript levels and activating retinoic acid (RA) signaling, while reducing CD24+/CD44+ populations. Based on these findings, we can infer that ALDH1A3 acts as a key regulator in breast cancer by controlling the balance between ALDH-positive tumor stem cells and CD24/CD44 markers. Additionally, it appears to influence the switch between epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET), as well as glucose metabolism. This suggests that ALDH1A3 plays a central role in tumor stemness, cellular plasticity, and energy metabolism in breast cancer progression (Fernando et al., 2024). In lung cancer, international researchers have found that TMPRSS4 induces cancer stem cell properties in lung cancer cells. Studies also show

this protein is linked to ALDH expression in non-small cell lung cancer (NSCLC) patients. This suggests TMPRSS4 may play an important role in maintaining cancer stemness through regulating ALDH activity. The findings indicate that TMPRSS4 could be a potential marker for cancer stem cells in NSCLC, and may contribute to tumor progression and treatment resistance (de Aberasturi et al., 2016). In lung cancer, international researchers have found that TMPRSS4 induces cancer stem cell properties in lung cancer cells. Studies also show this protein is linked to ALDH expression in non-small cell lung cancer (NSCLC) patients. This suggests TMPRSS4 may play an important role in maintaining cancer stemness through regulating ALDH activity. The findings indicate that TMPRSS4 could be a potential marker for cancer stem cells in NSCLC, and may contribute to tumor progression and treatment resistance(Read et al., 2021). To date, research on esophageal cancer-related genes remains limited, though studies confirm the presence of various alcohol dehydrogenase (ADH) isozymes and ALDHs in human esophageal mucosa (Jelski et al., 2009b), ADHs and ALDHs are key enzymes in ethanol metabolism. A follow-up study of 59 esophageal cancer patients (27 adenocarcinomas, 32 squamous cell carcinomas) revealed that increased ADH IV activity may exacerbate carcinogenesis by enhancing the conversion of ethanol to acetaldehyde(Jelski et al., 2009a),thereby promoting esophageal cancer.

In addition, domestic scholars have investigated the mechanism by which microRNAs regulate the biological behavior of tumor cells via ALDH1 in fibrosarcoma (Cheng et al., 2024). Experimental results show that compared with normal tissues or cells, miR-761 expression is significantly downregulated in both osteosarcoma tissues and cell lines. Importantly, miR-761 levels show a negative correlation with ALDH1B1 expression. Furthermore, clinical data reveals that lower miR-761 expression is closely associated with several poor prognosis factors in patients, including tumor metastasis, disease recurrence, shorter overall survival, and advanced Enneking staging (GTM stage). These findings suggest that miR-761 may serve as a potential tumor suppressor in osteosarcoma progression (Wang, 2022). Glioblastoma (GBM) is the most aggressive subtype of glioma, mainly due to its unique population of glioma stem cells (GSCs). These GSCs have special abilities that make the cancer particularly dangerous, including self-renewal, differentiation into heterogeneous tumor cells, tissue invasion, and resistance to treatments (Alves et al., 2021; Tang et al., 2021),Research shows that ALDH1A1 plays a key role in these aggressive characteristics - it's primarily responsible for GSCs' invasive growth patterns and their resistance to both chemotherapy and radiation therapy. This explains why GBM is so difficult to treat effectively (Abu-Serie et al., 2024). Research has shown that ALDH1A1 contributes to drug resistance in chemotherapy and radiation therapy through multiple mechanisms. First, it directly inactivates therapeutic drugs. Second, it increases the expression of ABC (ATP-binding cassette) transporters, which help remove drugs from cancer cells. Third, it neutralizes harmful reactive oxygen species generated during treatment. Because of these important functions, ALDH1A1 plays a key role in treatment resistance. This makes it a promising therapeutic target - if we can block ALDH1A1 activity, we may be able to make cancer cells more sensitive to standard treatments (Crunkhorn, 2022). In summary, we can clearly see that members of the ALDHs family are increasingly being recognized for their important roles in malignant tumors. Growing evidence shows these enzymes participate in multiple cancer-related processes, from tumor development to treatment resistance. As researchers continue to investigate,

the significance of ALDHs in cancer biology is becoming more apparent. This understanding opens new possibilities for developing targeted therapies against various cancers.

2.3. Relevance Between ALDH1B1 and the Development of Colorectal Cancer

2.3.1. Incidence of Colorectal Cancer

Colorectal cancer (CRC) ranks among the most prevalent malignancies worldwide, accounting for approximately 1/10 of all cancer cases and cancer-related deaths. Notably, the incidence of early-onset CRC (diagnosis age <50 years) has been increasing by 1%-4% annually in many countries (Qiu et al., 2021). In 2022 alone, an estimated 151, 030 new CRC cases were projected to be diagnosed, including 44,850 rectal cancer cases. While developed nations have witnessed stabilized incidence rates (attributed to widespread screening), developing countries like China have shown an upward trend with a distinct shift toward younger populations (Lang & Ciombor, 2022). The etiology of CRC is multifactorial, primarily involving chronic inflammation induced by gastrointestinal infections, immune system dysregulation, environmental factors, and dietary habits. Such chronic inflammation drives inflammation-associated tumorigenesis by inducing DNA damage or silencing tumor suppressor genes (Colotta et al., 2009). The recruitment of inflammatory immune cells to tumor sites further facilitates tumor progression and distant metastasis. Importantly, treatment-induced inflammation significantly influences therapeutic response and recurrence, exerting substantial impacts on CRC prognosis (Ghiringhelli & Fumet, 2019). Consequently, identifying reliable biomarkers for predicting recurrence and mortality risks becomes imperative to enable early intervention and alleviate the growing global burden of CRC.

2.3.2. Cancerous Transformation Process

Emerging research reveals that eukaryotic initiation factor 4E (EIF4E) exhibits unexpected non-translational functions in cancer cells, rendering malignant cells particularly susceptible to ferroptosis. EIF4E physically interacts with ALDH1B1 in membranes—especially mitochondrial-associated membranes—to restrict ALDH1B1-mediated clearance of 4-hydroxynonenal (4HNE), which is not only a lipid peroxidation byproduct but also a key mediator of ferroptosis (Chen et al., 2022). Ferroptosis occurs in both normal and tumor cells via RAS-dependent or RAS-independent mechanisms(Xie et al., 2016).During carcinogenesis, genetic alterations include oncogene activation (KRAS, CMYC, EGFR), tumor suppressor gene inactivation (APC, DCC, TP53), mismatch repair gene mutations (HMSH1, HLH1, PMS1, PMS2, GTBP), and gene overexpression (COX-2, CD44v). Among these, KRAS mutations represent the most frequent aberrations. Direct targeting of KRAS remains challenging due to its resistance to small-molecule inhibition (Negri et al., 2022). Notably, over 20% of human cancers harbor mutations in one of the three RAS oncogenes (HRAS, KRAS, NRAS), making RAS the most prevalent oncogenic driver (Colicelli, 2004), and the most commonly mutated gene family in human cancers. The primary downstream effector of RAS is the MAPK/ERK (extracellular signal-regulated kinase) signaling cascade, which regulates normal cellular processes such as growth, differentiation, inflammation, and apoptosis. The PI3K pathway, the second major RAS effector, modulates cell growth, cycle progression, survival, cytoskeletal reorganization, and metabolism(Negri et al., 2022).

2.3.3. Pathway of ALDH1B1 Carcinogenesis

Furthermore, dysregulation of other oncogenic signaling pathways has been implicated in colorectal cancer (CRC). Mutation-induced constitutive activation of the Wnt/β-catenin pathway is considered the most prominent event, where pathway activation prevents Axin-dependent phosphorylation and degradation of β-catenin(Reya & Clevers, 2005).The accumulated free β-catenin translocates to the nucleus, where it binds and activates T-cell factor (TCF)/lymphoid enhancer factor (LEF) transcription factors(Daniels & Weis, 2005).Studies demonstrate that ALDH1B1 plays a critical role in cell survival and proliferation by modulating the Wnt/β-catenin, Notch, and PI3K/Akt signaling pathways, ALDH1B1 contributes to a pro-tumorigenic microenvironment in colon cancer cells by metabolizing retinaldehyde to generate retinoic acid (RA). When RA binds to FABP5 (which is highly expressed in colon cancer cells), it activates PPARβ/δ, thereby upregulating the PI3K/Akt pathway, which suppresses β-catenin degradation and promotes its nuclear translocation. Furthermore, ALDH1B1 knockout leads to the downregulation of key Wnt/β-catenin signaling proteins (such as active β-catenin and LEF1) and downstream target genes (including c-Myc and LGR5), while increasing the expression of the negative regulator Axin2. Additionally, ALDH1B1 activates Notch signaling (evidenced by increased Notch1 cleavage) via Wnt-dependent upregulation of JAG1, establishing a Wnt-Notch positive feedback loop that synergistically enhances cell proliferation and tumorigenesis. Thus, ALDH1B1 stabilizes β-catenin through the "RA-FABP5-PPARβ/δ-PI3K/Akt" axis and cooperates with the Notch pathway to collectively drive colon cancer development(Singh, Arcaroli, et al., 2015).The Notch pathway is pivotal in embryogenesis, cellular homeostasis, differentiation, epithelial-mesenchymal transition (EMT), and apoptosis(Yuan et al., 2015). Notably, cancer stem cells exhibit 10- to 30-fold higher Notch signaling activity compared to bulk tumor cells, correlating with their superior proliferative potential and chemoresistance(Gupta et al., 2019).The Wnt signaling cascade comprises three major branches: (1) the non-canonical planar cell polarity pathway regulating cytoskeletal organization; (2) the non-canonical Wnt/calcium pathway modulating intracellular calcium levels; and (3) the canonical Wnt pathway, which involves β-catenin-dependent activation of the TCF-LEF transactivation complex and is strongly associated with tumorigenesis (Takebe et al., 2015).Among these, canonical Wnt signaling is the best characterized and has been a major focus of therapeutic inhibition for cancer and other diseases. Additionally, the PI3K/AKT pathway contributes to CRC progression primarily through proprotein convertase subtilisin/kexin type 9 (PCSK9)-mediated regulation of EMT induction and PI3K/AKT signaling in tumor cells, as well as via macrophage phenotypic polarization modulated by macrophage migration inhibitory factor (MIF) and lactate levels (Wang et al., 2022).

Research in colorectal cancer has revealed that ALDH1B1, a mitochondrial aldehyde dehydrogenase isozyme, shows significant overexpression strongly correlated with cancer initiation, progression, and treatment resistance. This enzyme drives tumor growth through three key mechanisms: (1) enhancing cancer cell survival, (2) promoting uncontrolled proliferation, and (3) developing resistance to chemotherapeutic agents, particularly 5-fluorouracil (5-FU) - a first-line treatment for colorectal cancer (Crunkhorn, 2022). These findings demonstrate ALDH1B1's

multifaceted role in making colorectal cancers more aggressive and treatment-resistant.Further studies show that ALDH1B1 deficiency significantly inhibits the growth of APC mutation-driven colorectal adenomas, with particularly noticeable reduction in macroscopic colon adenomas. This evidence suggests that ALDH1B1 likely promotes colorectal cancer development by regulating the β-catenin/Wnt signaling pathway, a crucial pathway for cancer growth (Golla et al., 2020).

International experimental studies have demonstrated that ALDH1B1 closely interacts with numerous proteins involved in both single-strand break and double-strand break repair processes, suggesting its potential critical role in DNA damage response (DDR) and DNA repair mechanisms (Tsochantaridis et al., 2022). Emerging evidence indicates ALDH1B1 may serve as a potential biomarker for colorectal cancer (CRC), as its expression pattern shows strong correlation with activation of the Wnt/β-catenin signaling pathway - a key driver of colorectal carcinogenesis. Since Wnt signaling activation is mediated through β-catenin binding to TCF/LEF transcription factors, the presence of TCF-binding elements (TBEs) in promoter regions becomes essential for all genes directly regulated by this pathway (Wang et al., 2023). Emerging studies have identified AMBRA1 as a tumor suppressor that negatively regulates ALDH1B1 function through non-canonical ubiquitination (K27/K33 linkages). This ubiquitination is mediated by the cooperative action of AMBRA1 with E3 ligases TRAF6/DDB1, which specifically target lysine residues K506/K511/K515 on ALDH1B1 to induce K27/K33-linked polyubiquitination. This post-translational modification disrupts ALDH1B1 homotetramer formation and consequently reduces its enzymatic activity. Following ALDH1B1 functional impairment, expression of its downstream target PTEN (a negative regulator of β-catenin) is upregulated, while β-catenin and its target genes (including c-Myc and LGR5) are downregulated, ultimately suppressing the Wnt/β-catenin signaling pathway (Baek & Jang, 2021).While substantial research data support a potential association between ALDH1B1 and CRC development, the clinical relevance of its expression pattern as a prognostic indicator remains controversial and requires further validation.

3. Prospects and Future of ALDH1B1

The scientific community currently recognizes cancer stem cells (CSCs) as the primary drivers of tumor progression and recurrence. This understanding has prompted researchers to focus on ALDH1B1, given its potential role in regulating the functionality of colorectal cancer stem cells. ALDH1B1 warrants investigation because, similar to CSCs, it exhibits self-renewal and multipotent differentiation capabilities. Building upon this discovery, we aim to further examine ALDH1B1 expression patterns in colorectal cancer and elucidate their relationship with CSCs. Such studies may also evaluate ALDH1B1's potential as a novel therapeutic target for CSC-associated colorectal cancer treatment.

Current research suggests that ALDH1B1 shows promise as a potential biomarker for early-stage colorectal cancer (CRC) patients. Recent years have witnessed significant progress in research on ALDH1B1 (aldehyde dehydrogenase 1B1) as a potential biomarker for colorectal cancer (CRC), demonstrating particular value in early diagnosis, prognostic evaluation, and personalized therapy. ALDH1B1 exhibits a highly specific expression pattern - while being

restricted to the stem cell zone at the crypt base in normal colon tissue, it shows widespread overexpression in colorectal cancer tissues. This distinct expression profile makes it a promising target for early screening applications. A retrospective cohort study of 315 patients with colorectal lesions (130 CRC cases, 75 high-grade adenomas, and 110 healthy controls)(Wang et al., 2020) revealed significantly elevated serum anti-ALDH1B1 autoantibodies in both colorectal cancer (AUC=0.70) and high-grade adenoma (AUC=0.74) groups ($p<0.001$). The autoantibody demonstrated 62.3% sensitivity for early CRC detection, substantially outperforming the conventional marker CEA (38.6%). Western blot validation further confirmed that ALDH1B1 autoantibody levels were even higher in precancerous lesions (high-grade adenomas) than in CRC, suggesting its potential as a continuous monitoring marker from precancerous stages. Multi-marker analysis showed that combining ALDH1B1 with CTAG1 and CENPF improved diagnostic performance to AUC=0.79 (95%CI: 0.71-0.85). This study represents the first large-scale serum proteomic analysis to demonstrate the unique value of ALDH1B1 autoantibodies in early colorectal cancer screening and precancerous lesion detection. A retrospective cohort study (n=30 CRC patients) (Langan et al., 2012)demonstrated that ALDH1B1 expression significantly correlates with tumor differentiation and histological type, showing markedly higher levels in poorly/moderately differentiated tumors compared to well-differentiated or mucinous adenocarcinomas ($p=0.011$). Notably, metastatic tumors exhibited significantly elevated ALDH1B1 expression versus normal colon tissue ($p=0.001$), suggesting its potential as a progression biomarker. Nested case-control analyses of international biobanks revealed that serum ALDH1B1 levels are already elevated in precancerous conditions (e.g., high-grade adenomas), indicating its promise as a non-invasive liquid biopsy marker. Furthermore, high ALDH1B1 expression strongly associates with poor prognosis in CRC patients and may serve as an independent risk stratification indicator. TCGA (The Cancer Genome Atlas) database analysis identified that elevated ALDH1B1 mRNA expression correlates with increased recurrence risk in microsatellite-stable (MSS) CRC ($p=0.003$), particularly within lymph node metastasis subgroups. Collectively, these findings raise the crucial question of whether ALDH1B1 influences chemoresistance through cancer stem cell regulation, which represents a key objective for future personalized therapy research. Based on current large-scale evidence, ALDH1B1 demonstrates clear translational potential as a CRC biomarker, especially for early screening and prognostic stratification. Prospective intervention studies (e.g., NCI's PROSPECT trial) are warranted to validate clinical utility and explore ALDH1B1-targeted strategies (e.g., small-molecule inhibitors or combination immunotherapies). Breakthroughs in this direction may provide novel tools for CRC precision medicine.

Emerging studies have established an association between ALDH1B1 and colorectal cancer (CRC) development. However, the precise mechanisms through which this protein influences carcinogenesis and the specific biochemical pathways involved remain incompletely understood. To elucidate ALDH1B1's role in CRC pathogenesis, researchers must conduct additional experimental investigations and implement long-term patient follow-up studies. A deeper understanding of ALDH1B1's functional characteristics and expression patterns could open new therapeutic avenues for CRC management. Such advances may facilitate earlier cancer detection and enable personalized treatment strategies tailored to individual patients. It should be

emphasized, however, that these potential applications require further experimental validation through robust clinical studies.

Author Contributions:

Writing ─ original draft preparation, Chi Gao; writing ─ review and editing, Jianwei Qiao, Weijie Li; supervision: Zhihui Tai. All authors have read and agreed to the published version of the manuscript.

Funding:

No funding was received for this study.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Acknowledgments:

We apologize to the colleagues whose work could not be cited here due paper length restraints.

Conflict of Interest:

The authors declare no conflict of interest.

References

Abu-Serie, M. M., Osuka, S., Heikal, L. A., Teleb, M., Barakat, A., & Dudeja, V. (2024). Diethyldithiocarbamate-ferrous oxide nanoparticles inhibit human and mouse glioblastoma stemness: aldehyde dehydrogenase 1A1 suppression and ferroptosis induction. Front Pharmacol, 15, 1363511.

Alves, A. L. V., Gomes, I. N. F., Carloni, A. C., Rosa, M. N., da Silva, L. S., Evangelista, A. F., Reis, R. M., & Silva, V. A. O. (2021). Role of glioblastoma stem cells in cancer therapeutic resistance: a perspective on antineoplastic agents from natural sources and chemical derivatives. Stem Cell Res Ther, 12(1), 206.

Baek, S. H., & Jang, Y. K. (2021). AMBRA1 Negatively Regulates the Function of ALDH1B1, a Cancer Stem Cell Marker, by Controlling Its Ubiquitination. Int J Mol Sci, 22(21), 12079.

Chen, X., Huang, J., Yu, C., Liu, J., Gao, W., Li, J., Song, X., Zhou, Z., Li, C., Xie, Y., Kroemer, G., Liu, J., Tang, D., & Kang, R. (2022). A noncanonical function of EIF4E limits ALDH1B1 activity and increases susceptibility to ferroptosis. Nat Commun, 13(1), 6318.

Cheng, X., Xu, J., Gu, H., Chen, G., & Wu, L. (2024). ALDH1+ tumor stem cells promote the progression of malignant fibrous tissue sarcoma by inhibiting SYNPO2 through hsa-mir-206. Exp Cell Res, 441(1), 114167.

Colicelli, J. (2004). Human RAS superfamily proteins and related GTPases. Sci STKE, 2004(250), 13.

Colotta, F., Allavena, P., Sica, A., Garlanda, C., & Mantovani, A. (2009). Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis, 30(7), 1073-1081.

Crunkhorn, S. (2022). Targeting ALDH1B1 in colorectal cancer. Nat Rev Drug Discov, 21(9), 636.

Daniels, D. L., & Weis, W. I. (2005). Beta-catenin directly displaces Groucho/TLE repressors from Tcf/Lef in Wnt-mediated transcription activation. Nat Struct Mol Biol, 12(4), 364-371.

de Aberasturi, A. L., Redrado, M., Villalba, M., Larzabal, L., Pajares, M. J., Garcia, J., Evans, S. R., Garcia-Ros, D., Bodegas, M. E., Lopez, L., Montuenga, L., & Calvo, A. (2016). TMPRSS4 induces cancer stem cell-like properties in lung cancer cells and correlates with ALDH expression in NSCLC patients. Cancer Lett, 370(2), 165-176.

Feng, Z., Hom, M. E., Bearrood, T. E., Rosenthal, Z. C., Fernández, D., Ondrus, A. E., Gu, Y., McCormick, A. K., Tomaske, M. G., Marshall, C. R., Kline, T., Chen, C. H., Mochly-Rosen, D., Kuo, C. J., & Chen, J. K. (2022). Targeting colorectal cancer with small-molecule inhibitors of ALDH1B1. Nat Chem Biol, 18(10), 1065-1075.

Fernando, W., Cruickshank, B. M., Arun, R. P., MacLean, M. R., Cahill, H. F., Morales-Quintanilla, F., Dean, C. A., Wasson, M. D., Dahn, M. L., Coyle, K. M., Walker, O. L., Power Coombs, M. R., & Marcato, P. (2024). ALDH1A3 is the switch that determines the balance of ALDH(+) and CD24(-)CD44(+) cancer stem cells, EMT-MET, and glucose metabolism in breast cancer. Oncogene, 43, 3151-3169.

Ghiringhelli, F., & Fumet, J. D. (2019). Is There a Place for Immunotherapy for Metastatic Microsatellite Stable Colorectal Cancer? Front Immunol, 10, 1816.

Golla, J. P., Kandyliari, A., Tan, W. Y., Chen, Y., Orlicky, D. J., Thompson, D. C., Shah, Y. M., & Vasiliou, V. (2020). Interplay between APC and ALDH1B1 in a newly developed mouse model of colorectal cancer. Chem Biol Interact, 331, 109274.

Gupta, R., Bhatt, L. K., Johnston, T. P., & Prabhavalkar, K. S. (2019). Colon cancer stem cells: Potential target for the treatment of colorectal cancer. Cancer Biol Ther, 20(8), 1068-1082.

Hwang, C. C., Nieh, S., Lai, C. H., Tsai, C. S., Chang, L. C., Hua, C. C., Chi, W. Y., Chien, H. P., Wang, C. W., Chan, S. C., Hsieh, T. Y., & Chen, J. R. (2014). A retrospective review of the prognostic value of ALDH-1, Bmi-1 and Nanog stem cell markers in esophageal squamous cell carcinoma. PLoS One, 9(8), e105676.

Jelski, W., Kozlowski, M., Laudanski, J., Niklinski, J., & Szmitkowski, M. (2009a). The activity of class I, II, III, and IV alcohol dehydrogenase (ADH) isoenzymes and aldehyde dehydrogenase (ALDH) in esophageal cancer. Dig Dis Sci, 54(4), 725-730.

Jelski, W., Kozlowski, M., Laudanski, J., Niklinski, J., & Szmitkowski, M. (2009b). Alcohol dehydrogenase isoenzymes and aldehyde dehydrogenase activity in the sera of patients with esophageal cancer. Clin Exp Med, 9(2), 131-137.

Lang, D., & Ciombor, K. K. (2022). Diagnosis and Management of Rectal Cancer in Patients Younger Than 50 Years: Rising Global Incidence and Unique Challenges. J Natl Compr Canc Netw, 20(10), 1169-1175.

Langan, R. C., Mullinax, J. E., Ray, S., Raiji, M. T., Schaub, N., Xin, H. W., Koizumi, T., Steinberg, S. M., Anderson, A., Wiegand, G., Butcher, D., Anver, M., Bilchik, A. J., Stojadinovic, A., Rudloff, U., & Avital, I. (2012). A Pilot Study Assessing the Potential Role of non-CD133 Colorectal Cancer Stem Cells as Biomarkers. J Cancer, 3, 231-240.

Lavudi, K., Nuguri, S. M., Pandey, P., Kokkanti, R. R., & Wang, Q. E. (2024). ALDH and cancer stem cells: Pathways, challenges, and future directions in targeted therapy. Life Sci, 356, 123033.

Marcato, P., Dean, C. A., Liu, R. Z., Coyle, K. M., Bydoun, M., Wallace, M., Clements, D., Turner, C., Mathenge, E. G., Gujar, S. A., Giacomantonio, C. A., Mackey, J. R., Godbout, R., & Lee, P. W. (2015). Aldehyde dehydrogenase 1A3 influences breast cancer progression via differential retinoic acid signaling. Mol Oncol, 9(1), 17-31.

Muzio, G., Maggiora, M., Paiuzzi, E., Oraldi, M., & Canuto, R. A. (2012). Aldehyde dehydrogenases and cell proliferation. Free Radic Biol Med, 52(4), 735-746.

Negri, F., Bottarelli, L., de'Angelis, G. L., & Gnetti, L. (2022). KRAS: A Druggable Target in Colon Cancer Patients. Int J Mol Sci, 23(8), 4120.

Qiu, C., Shi, W., Wu, H., Zou, S., Li, J., Wang, D., Liu, G., Song, Z., Xu, X., Hu, J., & Geng, H. (2021). Identification of Molecular Subtypes and a Prognostic Signature Based on Inflammation-Related Genes in Colon Adenocarcinoma. Front Immunol, 12, 769685.

Read, E., Milford, J., Zhu, J., Wu, L., Bilodeau, M., & Yang, G. (2021). The interaction of disulfiram and H(2)S metabolism in inhibition of aldehyde dehydrogenase activity and liver cancer cell growth. Toxicol Appl Pharmacol, 426, 115642.

Reya, T., & Clevers, H. (2005). Wnt signalling in stem cells and cancer. Nature, 434(7035), 843-850.

Singh, S., Arcaroli, J., Chen, Y., Thompson, D. C., Messersmith, W., Jimeno, A., & Vasiliou, V. (2015). ALDH1B1 Is Crucial for Colon Tumorigenesis by Modulating Wnt/ β -Catenin, Notch and PI3K/Akt Signaling Pathways. PLoS One, 10(5), e0121648.

Singh, S., Chen, Y., Matsumoto, A., Orlicky, D. J., Dong, H., Thompson, D. C., & Vasiliou, V. (2015). ALDH1B1 links alcohol consumption and diabetes. Biochem Biophys Res Commun, 463(4), 768-773.

Sun, N., Cai, Q., Zhang, Y., Zhang, R. R., Jiang, J., Yang, H., Qin, C. F., & Cheng, G. (2024). The aldehyde dehydrogenase ALDH1B1 exerts antiviral effects through the aggregation of the adaptor MAVS. Sci Signal, 17(818), eadf8016.

Takebe, N., Miele, L., Harris, P. J., Jeong, W., Bando, H., Kahn, M., Yang, S. X., & Ivy, S. P. (2015). Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: clinical update. Nat Rev Clin Oncol, 12(8), 445-464.

Tang, X., Zuo, C., Fang, P., Liu, G., Qiu, Y., Huang, Y., & Tang, R. (2021). Targeting Glioblastoma Stem Cells: A Review on Biomarkers, Signal Pathways and Targeted Therapy. Front Oncol, 11, 701291.

Toledo-Guzmán, M. E., Hernández, M. I., Gómez-Gallegos Á, A., & Ortiz-Sánchez, E. (2019). ALDH as a Stem Cell Marker in Solid Tumors. Curr Stem Cell Res Ther, 14(5), 375-388.

Tran, T. O., Vo, T. H., Lam, L. H. T., & Le, N. Q. K. (2023). ALDH2 as a potential stem cell-related biomarker in lung adenocarcinoma: Comprehensive multi-omics analysis. Comput Struct Biotechnol J, 21, 1921-1929.

Tsochantaridis, I., Kontopoulos, A., Voulgaridou, G. P., Tsifintaris, M., Triantafyllou, C., & Pappa, A. (2022). Aldehyde Dehydrogenase 1B1 Is Implicated in DNA Damage Response in Human Colorectal Adenocarcinoma. Cells, 11(13), 2017 .

Tsochantaridis, I., Roupas, A., Voulgaridou, G. P., Giatromanolaki, A., Koukourakis, M. I., Panayiotidis, M. I., & Pappa, A. (2021). Aldehyde Dehydrogenase 1B1 Is Associated with Altered Cell Morphology, Proliferation, Migration and Chemosensitivity in Human Colorectal Adenocarcinoma Cells. Biomedicines, 9(1), 44.

Wang, H., Zhang, B., Li, X., Zhou, D., Li, Y., Jia, S., Qi, S., Xu, A., Zhao, X., Wang, J., Bai, Z., Cao, B., Li, N., Dai, M., Chen, H., & Huang, J. (2020). Identification and Validation of Novel Serum Autoantibody Biomarkers for Early Detection of Colorectal Cancer and Advanced Adenoma. Front Oncol, 10, 1081.

Wang, L., Li, S., Luo, H., Lu, Q., & Yu, S. (2022). PCSK9 promotes the progression and metastasis of colon cancer cells through regulation of EMT and PI3K/AKT signaling in tumor cells and phenotypic polarization of macrophages. J Exp Clin Cancer Res, 41(1), 303.

Wang, X. (2022). MicroRNA-761 inhibits osteosarcoma progress by targetingALDH1B1 [Doctor, https://link.cnki.net/doi/10.27466/d.cnki.gzzdu.2022.002914

Wang, Y., Popovic, Z., Charkoftaki, G., Garcia-Milian, R., Lam, T. T., Thompson, D. C., Chen, Y., & Vasiliou, V. (2023). Multi-omics profiling reveals cellular pathways and functions regulated by ALDH1B1 in colon cancer cells. Chem Biol Interact, 384, 110714.

Wood, J. C., Cohen, A. R., Pressel, S. L., Aygun, B., Imran, H., Luchtman-Jones, L., Thompson, A. A., Fuh, B., Schultz, W. H., Davis, B. R., & Ware, R. E. (2016). Organ iron accumulation in chronically transfused children with sickle cell anaemia: baseline results from the TWiTCH trial. Br J Haematol, 172(1), 122-130.

Xie, Y., Hou, W., Song, X., Yu, Y., Huang, J., Sun, X., Kang, R., & Tang, D. (2016). Ferroptosis: process and function. Cell Death Differ, 23(3), 369-379.

Yao, S., Chen, W., Zuo, H., Bi, Z., Zhang, X., Pang, L., Jing, Y., Yin, X., & Cheng, H. (2022). Comprehensive Analysis of Aldehyde Dehydrogenases (ALDHs) and Its Significant Role in Hepatocellular Carcinoma. Biochem Genet, 60(4), 1274-1297.

Yuan, X., Wu, H., Xu, H., Xiong, H., Chu, Q., Yu, S., Wu, G. S., & Wu, K. (2015). Notch signaling: an emerging therapeutic target for cancer treatment. Cancer Lett, 369(1), 20-27.

Zhao, R., Guo, Z., Lu, K., Chen, Q., Riaz, F., Zhou, Y., Yang, L., Cheng, X., Wu, L., Cheng, K., Feng, L., Liu, S., Wu, X., Zheng, M., Yin, C., & Li, D. (2024). Hepatocyte-specific NR5A2 deficiency induces pyroptosis and exacerbates non-alcoholic steatohepatitis by downregulating ALDH1B1 expression. Cell Death Dis, 15(10), 770.