Review

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ALDH Enzymes and Hematological Diseases: A Scoping Review of Literature

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Aldehyde dehydrogenases (ALDHs) constitute a group of enzymes that catalyze the oxidation of aldehydes to carboxylic acids. The human ALDH superfamily, including 19 different isoenzymes (ALDH1A1, ALDH1A2, ALDH1A3, AHDH1B1, ALDH1L1, ALDH1L2, ALDH2, ALDH3A1, ALDH3A2, ALDH3B1, ALDH3B2, ALDH4A1, ALDH5A1, ALDH6A1, ALDH7A1, ALDH8A1, ALDH9A1, ALDHA16A1, ALDH18A1), displays different key physiological and toxicological functions, with specific tissue expression and substrate specificity. Several studies have established that ALDH are interesting markers for the identification and quantification of human hematopoietic stem cells and cancer stem cells, notably leukemic stem cells. ALDH2 is the best-documented enzyme, in this family, as having an impact on hematology, particularly myeloid malignancies. ALDH2 mainly catalyzes the detoxification of toxic aldehydes (acetaldehyde, formaldehyde). For example, ALDH2 detoxifies formaldehyde, which is produced during the differentiation of hematopoietic progenitors. The trigger of alcohol dehydrogenase 5 (also known as formaldehyde dehydrogenase or S-nitrosoglutathione reductase, ADH5/FDH/GSNOR)/ALDH2 allows to eliminate formaldehyde and ensures normal hematopoiesis. Moreover, the ALDH2*2 variant allele is the most frequent ALDH2 variant, found in 35–45% of individuals of East Asian origin. It is associated with altered acetaldehyde metabolism and is involved in several hematological diseases (aplastic anemia, bone marrow failure, myelodysplastic syndrome). This review presents current knowledge of different members of the ALDH family and their involvement in normal and malignant hematopoiesis. Focus was brought to the ALDH2 isoenzyme in congenital (Fanconi anemia, Aplastic anemia, mental retardation, and dwarfism (AMeD) syndrome, and idiopathic aplastic anemia) and acquired (acute myeloid leukemia and myelodysplastic syndrome) hematological diseases. It also describes the possibilities of using ALDH as both a biomarker and therapeutic target, to identify and eradicate leukemic stem cells in malignant diseases.

Keywords: hematopoietic stem cell; biomarker; ALDH2 polymorphism; Fanconi anemia; leukemia

Introduction

The aldehyde dehydrogenase (*ALDH*) gene superfamily encodes enzymes involved in the detoxification of endogenous and exogenous aldehyde substrates [1]. There are 19 human *ALDH*-related genes, with variable tissue expression and substrate specificity (Table 1, Ref. [2–27]). Multiple functions have been described for ALDH enzymes, respectively catalytic properties and non-catalytic interactions with both endogenous compounds and exogenous agents [1,28]. Endogenous aldehydes are produced through the metabolism of amino acids, carbohydrates, lipids, biogenic amines, vitamins, and steroids [28]. Furthermore, polymorphisms of human *ALDH* genes are frequently associated with metabolic disorders [29]. For example, *ALDH2* polymorphism is associated with altered acetaldehyde metabolism [29] as well as with an increased risk of oropharyngolaryngeal [30,31] or esophageal cancer [30,32]. Moreover, the loss of enzymatic activity induced by a polymorphism in *ALDH3A2* has been described in the Sjögren-Larsson syndrome [29,33,34].

ALDH2 is the best-documented enzyme, in the ALDH family, as having an impact on hematology. This enzyme, known to be mainly located in mitochondria, is encoded in humans by a nuclear gene located at the chromosome locus 12q24 [35]. ALDH2 expression is ubiquitous but displays a higher abundance in liver cells [36]. The role of this enzyme in alcohol metabolism has been well described. In humans, ethanol catabolism occurs in the liver, catalyzed by alcohol dehydrogenase (ADH) which transforms ethanol into acetaldehyde, and then by ALDH2 which transforms acetaldehyde into acetate [37], thus providing an essential protective enzymatic function against toxic agents. Other

Table 1. Human aldehyde dehydrogenase (ALDH) isoenzymes in hematology.

ALDH human gene	Location*	Subcellular localization	Preferred substrates	Involvement in hematology	Characteristics	Cells/patients	References
ALDH1A1	9q21.13	C	retinal	normal hematopoiesis	marker of normal primitive progenitors	human BM and CB CD34+ cells	[3,27]
				normal hematopoiesis	inhibition induces HSC expansion	murine BM KSL cells/human CB CD34+ cells	[26]
				normal hematopoiesis	high expression in long-term HSCs	murine HSCs	[2,4]
				CLL	increased activity in high-risk patients	CLL patients	[11]
				NHL	resistance to chemotherapy and apoptosis, activation of NF-κB/STAT3 signaling	human NHL cell lines	[12,13]
			(E)-4-hydroxynon-2-enal malondialdehyde benzaldehyde	NHL	high expression associated with poor prognosis	NHL patients	[12]
				MM	increased activity in clonogenic MM progenitors	human MM cell lines/MM patients	[14]
				MM	increased activity in light chain restricted B cells	MM patients	[15]
				MM	increased activity related to tumor initiation and chromosomal instability signatures	human and murine MM cell lines/human MM cells	[15]
				AML	increased activity at diagnosis predicts relapse	AML patient with t(8;21)	[7]
				AML	low levels in good prognosis cytogenetics	AML patients/AML cell lines	[8]
				CML	high expression in the CD34+ population but not in the CD34+CD38- subset	CML patients/CML cell lines	[9]
				CML	ponatinib is more effective than imatinib in reducing the percentage of ALDH+ cells	CML patients/CML cell lines	[10]
				leukemia	mediation of IGF2BP1, a regulator of leukemia cell tumorigenicity	human leukemic cell lines	[19]
ALDH1A2	15q21.3	C	retinal	expressed in sites of hematopoiesis	expression to 2 genes over 15 zebrafish *Adhs*: *Adh1a2* and *Adh16a1*	zebrafish	[6]
				overexpression in T-ALL	antioxidant protection, promotion of aerobic glycolysis and energy production	ALL patients/human ALL cell lines/zebrafish	[20]
				high expression in AraC-resistant AML	AraC resistance	AML cell lines/AML patients	[21]
ALDH1A3	15q26.3	C	retinal, acetaldehyde				
ALDH1B1	9p13.1	M	retinal, acetaldehyde				
ALDH1L1	3q21.3	C	10-formyl tetrahydrofolate				
ALDH1L2	12q23.3	M	10-formyl tetrahydrofolate	AML	overexpression in leukemic cells induced by BM-MSCs	human AML cell lines	[17]

Table 1. Continued.

ALDH human gene	Location*	Subcellular localization	Preferred substrates	Involvement in hematology	Characteristics	Cells/patients	References
ALDH2	12q24.12	M	acetaldehyde, 4-hydroxynonenal, malondialdehyde formaldehyde	normal hematopoiesis	high expression in BM primitive progenitors	murine BM KSL cells	[26]
				normal hematopoiesis	expression in long-term HSCs	human and murine HSCs	[5]
				normal hematopoiesis/MDS	pesticide-induced decrease in BM-MSCs promotes DNA damage and defective support of primitive hematopoiesis. Decreased expression in MDS	human BM MSCs	[18]
				AML	overexpression in leukemic cells induced by BM-MSCs through the non-canonical TGF-β pathway	human AML cell lines	[17]
				AML	silencing causes accumulation of endogenous aldehydes, DNA cross inks and requires UBE2T and FANCL recruitment to maintain cell integrity	AML patients/AML cell lines	[16]
				Fanconi anemia	protection of HSCs against acetaldehyde toxicity	murine models of Fanconi anemia	[23]
				Fanconi anemia	accelerated progression in BM failure with defective ALDH2 variant	Fanconi patients	[24]
				AMeD syndrome	cooperation with ADH5 to detoxify formaldehyde	AMeD patients/human embryonic cell lines	[25]
ALDH3A1	17p11.2	C,N	aromatic, aliphatic aldehydes				
ALDH3A2	17p11.2	P	fatty aldehydes	AML	protection against oxidative death. Lethal when concomitant inhibition of GPX4	murine AML/human AML cell lines/AML patients	[22]
ALDH3B1	11q13.2	C	octanal				
ALDH3B2	11q13.2						
ALDH4A1	1p36.13	M	glutamate γ-semi-aldehyde				
ALDH5A1	6p22.2	M	succinate semi-aldehyde				
ALDH6A1	14q24.3	M	malonate semi-aldehyde				
ALDH7A1	5q31	C,M,N	α-aminoadipic semi-aldehyde	normal hematopoiesis	expression in long-term HSCs	human and murine HSCs	[5]
ALDH8A1	6q23.2	C	retinal				
ALDH9A1	1q23.2	C	γ-aminobutyl-aldehyde				
ALDH16A1	19q13.33			expressed in sites of hematopoiesis	expression of 2 genes over 15 zebrafish *Adhs*: *Adh1a2* and *Adh16a1*	zebrafish	[6]
ALDH18A1	10q24.3	M	glutamic γ-semi-aldehyde				

ADH, alcohol dehydrogenase; C, cytosol; M, mitochondria; N, nucleus; P, peroxisome; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; HSC, hematopoietic stem cell; BM, bone marrow; CB, cord blood; KSL, Kit+ Sca-1+ Lin- cells; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; MM, multiple myeloma; CML, chronic myeloid leukemia; ALL, acute lymphocytic leukemia; AraC, cytarabine; AML, acute myeloid leukemia; NF-κB, nuclear factor-kappa B; STAT3, Signal transducer and activator of transcription 3; UBE2T, ubiquitin-conjugating enzyme E2 T; FANCL, Fanconi anemia complementation group L; MDS, myelodysplastic syndrome; MSC, mesenchymal stromal cell; AMeD, Aplastic anemia, mental retardation, and dwarfism; TGF-β, transforming growth factor beta; GPX4, glutathione peroxidase 4. *updated according to the GRCh38.p14 reference genome (2022).

catalytic actions have been described. For example, ischemia and reperfusion produce reactive oxygen species (ROS) which induce lipid peroxidation with an increase of 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA). It has been reported that ALDH2 activation reduces the ensuing neurological impairment in rats, indicating a potential implication of ALDH2 in 4-HNE degradation [38]. Genetic polymorphisms of human *ALDH2* have been described [39,40]. The ALDH2*2 variant allele, which produces an ALDH2 protein with the E487K mutation, is the most frequent *ALDH2* variant, found in 35–45% of East Asian people [39,41]. This polymorphism induces a lower ALDH2 enzymatic activity and impairs alcohol metabolism after consumption of alcoholic beverages. *ALDH2* polymorphism has also been described as potentially involved in neurodegenerative diseases such as Alzheimer's disease [42,43], but also in heart failure [44] and an overall increased cancer risk in Asian populations [45,46]. Transgenic mice with *Aldh2* deficiency have been generated to recapitulate the induced phenotype: (i) *Aldh2* knockout induces hypersensitivity to ethanol, acetaldehyde accumulation and disturbance of oxidative metabolism [47], (ii) *Aldh2*^{E487K} knock-in mice display a lower ALDH2 enzymatic activity, higher acetaldehyde levels after ethanol consumption and increased ROS production after chemotherapy [48]. This enzyme also appears to be important in the hematopoietic system. It has been shown to be involved in the detoxification of toxic aldehydes produced during hematopoietic progenitor differentiation. ALDH2 therefore plays a role in maintaining functional hematopoiesis, but it is also involved in a number of hematological diseases [49].

This review focuses on ALDH, and notably ALDH2, in hematopoiesis and hematological diseases.

Activity and Functions of ALDH in the Normal Hematopoietic System

Numerous studies have established that ALDH is involved in the biology of hematopoietic stem cells (HSCs) and is an interesting marker for the identification and quantification of these cells. HSCs present a higher immunoreactivity for ALDH1 than other hematopoietic primitive cells [50], suggesting a potential role of this enzyme in HSC maintenance. ALDH1 immunoreactivity has been reported to be useful in identifying and sorting bone marrow (BM) human HSCs [50,51] as viable cells by flow cytometry [52]. Storms *et al*. [51] published an efficient strategy to isolate primitive HSCs using BODIPY-aminoacetaldehyde (BAAA), a fluorescent non-toxic substrate for ALDH, which freely diffuses into intact and viable cells. In the presence of ALDH, BAAA is converted into BODIPY-aminoacetate (BAA), a negatively charged product retained inside the cells. Intracellular accumulation of BAA leads to an increased fluorescence, and ALDH^{bright} cells can be segregated by flow cytometry cell sorting [3]. This assay has been reported to be inappropriate to identify murine HSCs [2].

ALDH1A1 is also a marker of normal primitive progenitors [3,53] yet its inhibition causes HSC expansion [26,53]. *Aldh1a1* is overexpressed in murine long-term HSCs [4], but *Aldh1a1*$^{-/-}$ mice do not show defects in HSCs [54,55], since upregulation of *Aldh3a1* compensates for its absence [54]. Both the ALDH1A1 and ALDH3A1 enzymes play a significant role in HSC biology, and their effects can be attributed, at least in part, to changes in the metabolism of ROS and reactive aldehydes [54]. A double invalidation of *Aldh1a1* and *Aldh3a1* induces a decrease in HSC numbers in newborn mice [56]. ALDH2 and ALDH1A7 are also expressed in murine and human long-term HSCs [5]. Finally, 2 of the 15 zebrafish *Aldh* genes (*Aldh1a2* and *Aldh16a1*) are expressed in sites of hematopoiesis [6]. ALDH also has a precise function in regulating the differentiation of HSCs. N,N-diethylaminobenzaldehyde (DEAB), an irreversible inhibitor of ALDH1A1 and ALDH2 [57], has been shown to delay the differentiation of human HSCs *via* a decrease in retinoic acid receptor-mediated signaling [3,26].

The identification of HSCs through BAAA staining has been used in the process of HSC transplantation to assess the quality of the HSC graft [58]. In this study, Lioznov *et al*. [58] suggested that quantification of ALDH activity in allogeneic HSC grafts could be a marker for HSC activity. They observed that patients who received a low quantity of ALDH^{bright} cells presented a loss of colony-forming unit granulocyte-macrophage (CFU-GM) potential and a delayed completion of full hematopoietic donor cell chimerism. Moreover, Fallon *et al*. [59] reported that the ALDH^{bright} cell population in peripheral blood (PB) mobilized progenitors was enriched in cells with an immature phenotype, able to generate long-term culture (LTC)-derived CFU, expand in primary and secondary LTC, and generate multiple cell lineages. Interestingly, these authors also showed that in patients receiving autologous PB-derived HSC transplantation, the number of infused ALDH^{bright} cells was highly correlated with the time to neutrophil and platelet engraftment [59].

Maintenance of the HSC pool relies on the capacity to metabolize toxins generated exogenously or endogenously, and on the ability to repair cellular damage [60]. ALDH2, crucial in the detoxification of aldehydes [61] is highly expressed in BM primitive progenitors [26]. Hematopoietic differentiation is likely to trigger the production of formaldehyde, which relies on the alcohol dehydrogenase 5 (ADH5)/ALDH2 complex for the maintenance of progenitor expansion [62] (Fig. 1, Ref. [62]). Over the past decade, it has been well-established that endogenous aldehydes are potent genotoxic agents threatening proper hematopoiesis. HSCs from elderly individuals exhibit reduced self-renewal and a preference for myeloid differentiation. Nevertheless,

the specific factors and mechanisms governing this critical transition remain unclear. Recently it has been shown that DNA damage caused by the formaldehyde derived from cell metabolism triggers the p53 response in HSCs, leading to accelerated aging [63].

Activity and Functions of ALDH under Pathological Conditions

ALDH as a Biomarker

Acute myeloid leukemias (AMLs) are hematopoietic malignancies characterized by an aberrant clonal expansion resulting in massive BM infiltration by immature leucoblasts. In 1994, leukemic cells able to initiate the hematopoietic malignancy were identified and named "leukemia-initiating cells" [64] now currently called "leukemic stem cells" (LSCs) [65]. As for normal HSCs, this fraction of AML cells is characterized by a $CD34^{pos}CD38^{neg}$ immunophenotype. They are able to generate leukemia after transplantation in immunodeficient mice [64,65] and a hierarchy of distinct LSC classes with decreasing self-renewal ability has been established [66]. It has also been reported that LSCs might be $CD34^{neg}$ [67,68]. LSCs are quiescent, which explains the difficulty in eradicating these cells with standard therapies that classically target proliferating cells [69], thus explaining AML relapses [27]. In order to estimate the LSCs burden and eradicate these cells, specific markers are required to target them. Both $CD34^{pos}CD38^{neg}$ HSCs and LSCs present high levels of ALDH activity, and the $ALDH^{bright}$ population of leukemic cells display a significantly higher adhesion to human BM mesenchymal stromal cells (MSCs), providing a basis for identifying and refining the combined immunophenotype and function of LSCs and HSCs in AML BM [70,71]. ALDH enzymatic activity could participate in chemoresistance since the transduction of human leukemic cells with lentiviral vectors encoding *ALDH1A2* or *ALDH2* increases resistance to doxorubicin and 4-hydroxypercyclophosphamide [72]. Moreover, in AML patients with t(8;21), a high aldehyde dehydrogenase activity at diagnosis could predict relapse [7]. Moreover, a correlation has been shown between AML with low levels of ALDH1A1 and good prognosis cytogenetics [8,73]. Since surface markers are missing to identify LSC [70,74], it has been suggested that ALDH activity could be used as a prognostic marker, also potentially useful for measurable residual disease (MRD) assessment [75].

Cells with high ALDH activity were also detected in samples from chronic myeloid leukemia (CML) patients [9]. The latter were consistently enriched in the $CD34^{pos}$ population but typically not in the $CD34^{pos}CD38^{neg}$ subset [9]. The Abelson 1 gene (ABL1)-specific tyrosine kinase inhibitors (TKI) are excellent treatments for CML patients in the chronic phase. The effects of imatinib (first-generation TKI) and ponatinib (third-generation TKI with a potentially higher activity on CML stem cells) were compared, showing that ponatinib was more effective than imatinib in reducing the percentage of $ALDH^{pos}$ cells in primary CML cells [10].

Finally, it has also been proposed to use ALDH activity as a biomarker in lymphoproliferative disorders. In chronic lymphocytic leukemia (CLL), a study evaluated whether increased ALDH activity was associated with a more aggressive disease [11]. Compared with two other CLL prognostic biomarkers (immunoglobulin heavy chain variable gene [IgHV] mutation status and *ZAP-70* expression), an increased ALDH activity was observed in high-risk CLL patients [11]. In concordance with this study, *ALDH1A1* expression has been reported to reduce the sensitivity of non-Hodgkin lymphoma (NHL) cell lines to the chemotherapeutic Cyclophosphamide - Hydroxydaunorubicine - Oncovin™ − Prednison regimen, with concomitant decreased apoptosis and activation of the nuclear factor-kappa B (NF-κB)/ Signal transducer and activator of transcription 3 (STAT3) signaling pathway [12,13]. High *ALDH1A1* expression was also shown to be associated with a poor prognosis in patients suffering from B-cell NHL [12,13], as well as in multiple myeloma (MM) drug-resistant progenitors [14,15,76].

ALDH Activity and Pathophysiology of Hematological Diseases

The involvement of endogenous aldehydes as major contributors to Fanconi anemia (FA), and the identification of a new BM failure syndrome termed Aplastic anemia, mental retardation, and dwarfism (AMeD) syndrome, due to a lack of enzymes clearing endogenous aldehydes, reinforce the significant pathological impact of aldehyde-induced genotoxicity [77].

Concerning AML cells, *ALDH2* silencing has been shown to lead to an accumulation of endogenous aldehydes, causing DNA cross-links and requiring the recruitment of FA proteins (ubiquitin-conjugating enzyme E2 T (UBE2T) and Fanconi anemia complementation group L (FANCL)) to maintain cell integrity [16]. This study suggests that pharmacologic inhibition of UBE2T/FANCL could be of interest for the elimination of ALDH2-deficient AML cells. Finally, the BM microenvironment could participate in the regulation of ALDH expression in leukemic cells since it has been shown that among the 19 ALDH isoforms, ALDH1L2 and ALDH2 are significantly overexpressed in human AML cells co-cultured with BM-MSCs compared to AML cells cultured alone [17]. In a recent study, our team observed that human normal BM-MSCs exposed to low doses of pesticides present a decreased ALDH2 activity associated with the accumulation of acetaldehyde, DNA damage and a decreased capacity to support primitive hematopoiesis [18]. Interestingly, the same abnormalities were found in primary BM-MSCs of patients suffering from myelodysplastic syndrome (MDS), a pre-leukemic myeloid

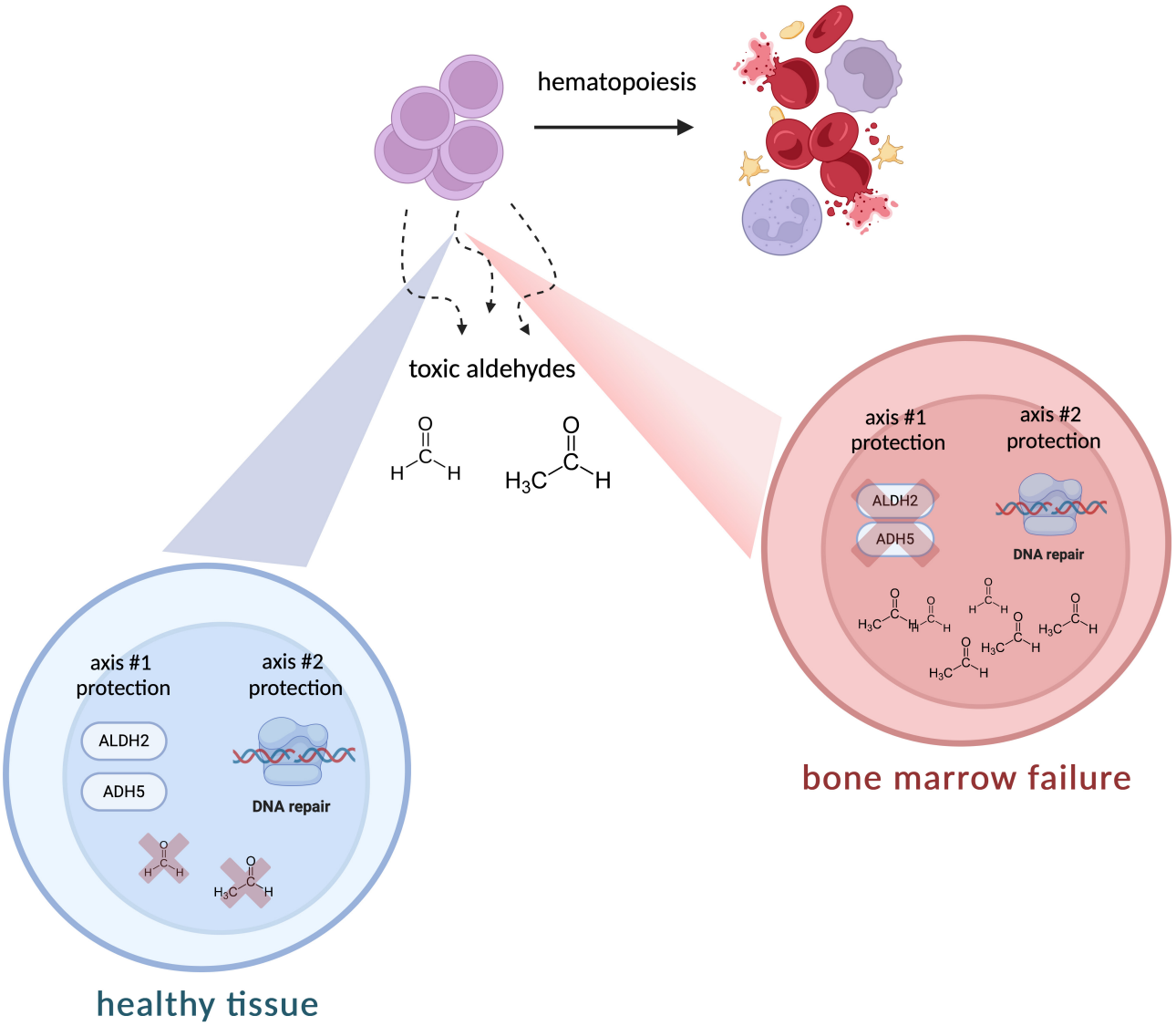

Fig. 1. The biological role of aldehyde dehydrogenase 2 (ALDH2) and alcohol dehydrogenase 5 (ADH5) in normal hematopoiesis and in bone marrow failure, (inspired by Mu *et al.* 2021 [62]). The alcohol dehydrogenase 5 (also known as formaldehyde dehydrogenase or S-nitrosoglutathione reductase, ADH5/FDH/GSNOR) and the ALDH2 are essential for the removal of toxic aldehydes, which are produced physiologically during hematopoiesis. In humans, the inability of ADH5 and ALDH2 to detoxify endogenous aldehydes can result in cytotoxicity, DNA damage and failure of hematopoietic stem cells, despite no evident defect in DNA repair mechanisms. Figure was created in https://BioRender.com.

disease occurring in elderly patients (over 55 years old), suggesting that ALDH2 deficiency in the BM microenvironment may participate in the pathophysiology of MDS, a pre-leukemic disease (Fig. 2, Ref. [7,17,18,24,25,78–80]).

Other ALDHs have been described as potentially involved in leukemia pathophysiology. While high *ALDH1* expression has been well-demonstrated to characterize immature progenitor cells in blood cancers (AML, CLL, MM), the differential expression of other *ALDH* isoforms is poorly described in hematological malignancies (Table 1). The team of Spiegelman reported that the levels of insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) affect both proliferation and the tumorigenic potential of leukemia cells, through the deregulation of *ALDH1A1* expression [19]. Moreover, *ALDH1A2* has been found to be aberrantly expressed in more than 50% of T-cell acute lymphoblastic leukemia (T-ALL) cases [20]. Besides, *ALDH1A2* expression confers resistance to aracytine in K562 leukemia cells and is increased after the appearance of aracytine resistance in clinical cases [21]. In murine models, *Aldh3a2* has been identified as critical in protecting LSCs from oxidative death and its inhibition is lethal when concomitant with the inhibition of glutathione peroxidase-4 [22].

In an attempt to selectively target the LSC population, ALDH inhibitors have been evaluated. Disulfiram

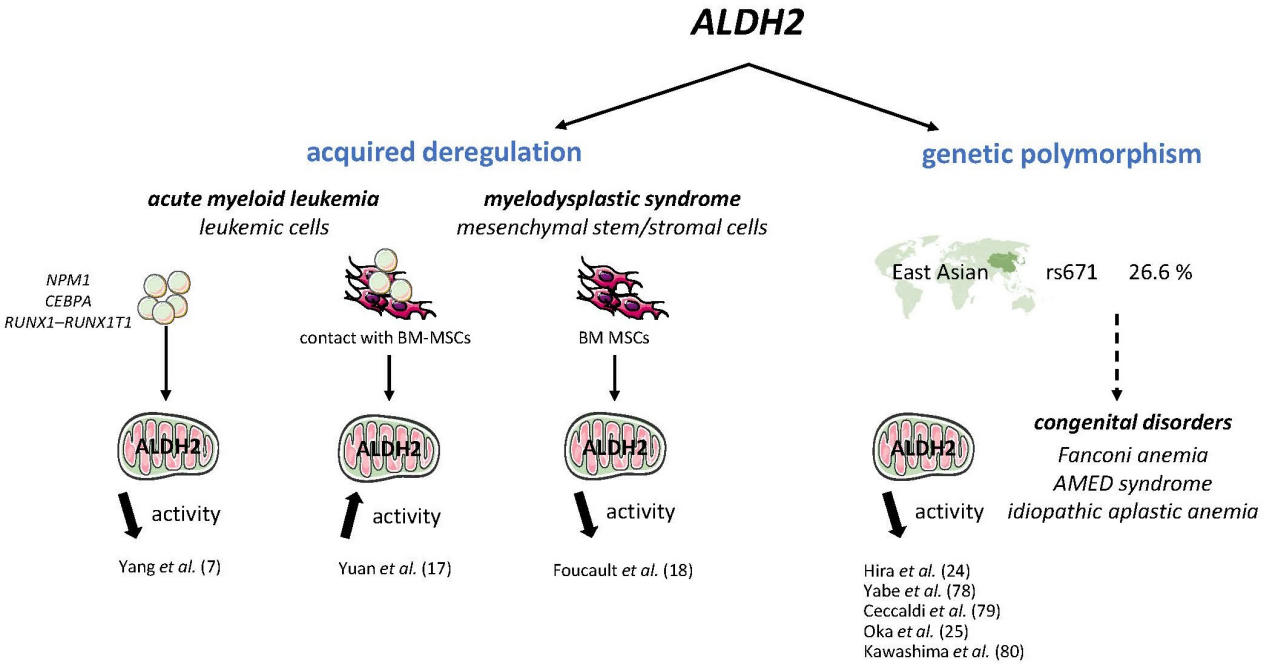

Fig. 2. Clinical significance of ALDH2 in hematological diseases. ALDH2 is deregulated in acute myeloid leukemia and myelodysplastic syndromes (acquired diseases). *ALDH2* polymorphism is associated with altered acetaldehyde metabolism, involved in congenital disorders such as Fanconi anemia, AMeD syndrome, and idiopathic aplastic anemia. AMeD, Aplastic anemia, mental retardation, and dwarfism; BM-MSCs, bone marrow mesenchymal stromal cells.

(DSF) has been reported to selectively eradicate LSCs in AML. This molecule is involved in cytotoxicity, involving the induction of the stress-related ROS-Jun N-terminal Kinase (JNK) pathway and inhibition of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and NF-κB pathways [81,82]. Another ALDH1 and ALDH3 inhibitor, dimethyl ampal thiolester (DIMATE), showed selective toxicity against LSCs without effects on normal HSCs [3, 83] while promoting a synergistic response with cytarabine [84]. Moreover, reactive oxygen species and ALDH1A1 can be used as prognosis and theragnostic biomarkers in AML patients [85,86].

Focus on ALDH2 in Hematological Diseases

The *ALDH2* human gene is located on chromosome locus 12q24.12, and it is interesting to note that abnormalities of chromosome 12q24 (addition, translocation, deletion) are widely described in such myeloid disorders as AML [87–90], CML [91,92], polycythemia vera, myelofibrosis [93] and MDS [94,95]. Nevertheless, these abnormalities have not yet been associated with ALDH2 dysfunctions.

ALDH2 Polymorphism

The *ALDH2* gene has many genetic polymorphisms. The rs671 mutation, also named Glu487Lys, Glu504Lys, or E504K and designated *ALDH2**2, is frequently found in East Asia [96,97] and encodes a protein with decreased ALDH2 activity [98]. This allele ALDH2 and more precisely the *ALDH2**2 allele is involved in the aging process [99,100]. Transgenic mice overexpressing *Aldh2**2 display a significantly decreased lifespan (median 96 weeks) compared to control mice (126 weeks) [101]. *ALDH2**2 allele has been described in hematological diseases and various cancers (Fig. 2) [45].

Very recently, new *ALDH2* variants, inducing a decreased ALDH2 functionality and an accumulation of cellular toxic acetaldehyde, have been reported among African (I41V mutation and *ALDH2**3 designation), Latino (P92T mutation and *ALDH2**4 designation or V304 mutation and *ALDH2**6 designation), South Asia (T244M mutation and *ALDH2**5 designation), and Finnish (R338W mutation and *ALDH2**7 designation) populations [102]. The medical consequences of these variants have not been reported to date.

ALDH2 and BM Failure (BMF)

The impact of an *ALDH2**2 allele was studied in relation to the clinical status of patients suffering from Diamond-Blackfan anemia (DBA), a very rare constitutional ribosomopathy inducing congenital anomalies, BMF and cancer predisposition. This disease is caused by alterations in ribosomal proteins encoding genes involved in erythropoiesis, notably *RPS19* (19q13) [103,104], with a

high rate of apoptosis in erythroid progenitors and precursors [105–107]. In the first year of life, DBA biological features are normochromic macrocytic anemia and reticulocytopenia associated with a decrease of erythroid precursors in the BM [108]. Ikeda *et al*. [109] studied a cohort of 113 DBA Japanese patients, 75 of them presenting with heterozygous mutations or deletions in ribosomal protein genes. No specificity was detected in DBA patients with *ALDH2* polymorphism related to age at onset, malformations or response to corticosteroids [109].

The impact of the *ALDH2* polymorphism rs671, c.1510G>A has also been studied in idiopathic aplastic anemia, another syndrome of BMF. AA homozygotes display very low aldehyde catalysis, and GA heterozygotes have strongly reduced catalysis compared with GG homozygotes. By studying 79 Japanese children (40 GG, 29 GA, 10 AA) aged $\leq$15 years with aplastic anemia, it was observed that patients with an AA genotype were significantly younger at diagnosis than GG or GA patients, without difference in the severity of the disease [80]. Moreover, the failure-free survival rate at 10 years was significantly decreased in the GA/AA group of patients [80]. Similarly, it has been shown that, in East Asia, the incidence of aplastic anemia in young adults is significantly higher than in Western countries [110–112].

FA is a rare autosomal recessive disorder associated with a genomic instability syndrome and characterized by BM failure (BMF), congenital abnormalities and cancer predisposition (in particular MDS, AML and solid tumors) [113–115]. Endogenous aldehydes are the major source of DNA damage repaired by the FA pathway. In this disease, ALDH2 protects the HSC pool against acetaldehyde toxicity [23]. The *ALDH2**2 allele has been associated with faster progression to BMF in children suffering from FA [24,78]. In ALDH2 deficient patients, HSCs accumulate DNA damage when both FA and DNA repair pathways are altered, causing BMF, mediated by p53/p21 signaling in cell death or senescence [79]. In Japanese children with FA, the median time to develop aplastic anemia is estimated at 28 months in heterozygous *ALDH2*/*ALDH2**2 patients and between 0 and 7 months in homozygous *ALDH2**2 patients *vs.* 72 months in homozygous wild-type *ALDH2* patients [24]. During pregnancy, both the mother and embryo produce endogenous aldehydes which can damage DNA. Maternal and embryonic ALDH2 are essential to repair DNA damage, specifically in *fanca*$^{-}$ deficient embryos [116–118]. This fetal aldehyde catabolism is essential for BM HSC preservation *in utero* [118]. It has been reported in mice, that *Aldh2*$^{-/-}$/*fanca*$^{-/-}$ embryo transfer in wild type mice avoids lethality but with impacting the HSCs pool [118]. Nevertheless, newborns present a BMF inducing death in less than 3 weeks [118].

A recent article published in 2020 has reported 10 cases of AMeD syndrome [25]. All patients developed MDS during infancy or childhood [25]. The authors showed that *ALDH2**2 polymorphism and biallelic mutations in *ADH5* were essential for AMeD syndrome development [25]. ALDH2 and ADH5 are two detoxifying enzymes essential in formaldehyde clearance. In case of deficiency of these two enzymes, formaldehyde accumulates in cells, leading to genome instability, hematopoietic failure and leukemia [49]. Concomitantly, it has also been reported that an *ALDH2**2 defective allele is involved in the severity of the clinical expression of AMeD syndrome [25,119].

Conclusions

ALDH isozymes display physiological and toxicological critical roles. This review highlights the key role of ALDH enzymes in hematologic diseases. ALDH2 deficient activity contributes to the severity of congenital BMF syndromes. Conversely, the high activity level of ALDH in LSCs from leukemic BM may help to identify these cells in flow cytometry assays. It also opens interesting therapeutic prospects for the pharmacological inhibition of these enzymes to eradicate these LSCs responsible for relapses which are the main concern of these leukemias.

Availability of Data and Materials

Not applicable.

Author Contributions

OH contributed to the conception of the research work. AF designed the research study and performed the research. OH supervised the work. AF drafted the manuscript and OH revised it critically. Both authors have read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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