IDH2: A novel biomarker for environmental exposure in blood circulatory system disorders (Review)

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Abstract. As the risk of harmful environmental exposure is increasing, it is important to find suitable targets for the diagnosis and treatment of the diseases caused. Isocitrate dehydrogenase 2 (IDH2) is an enzyme located in the mitochondria; it plays an important role in numerous cell processes, including maintaining redox homeostasis, participating in the tricarboxylic acid cycle and indirectly taking part in the transmission of the oxidative respiratory chain. IDH2 mutations promote progression in acute myeloid leukemia, glioma and other diseases. The present review mainly summarizes the role and mechanism of IDH2 with regard to the biological effects, such as the mitophagy and apoptosis of animal or human cells, caused by environmental pollution such as radiation, heavy metals and other environmental exposure factors. The possible mechanisms of these biological effects are described in terms of IDH2 expression, reduced nicotine adenine dinucleotide phosphate content and reactive oxygen species level, among other variables. The impact of environmental pollution on human health is increasingly attracting attention. IDH2 may therefore become useful as a potential diagnostic and therapeutic target for environmental exposure-induced diseases.

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Abbreviations: 2-HG, 2-hydroxyglutarate; α-KG, α-ketoglutarate; AITL, angioimmunoblastic T-cell lymphoma; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; GPX4, glutathione peroxidase 4; IDH, isocitrate dehydrogenase; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasia; $NADP^+$, nicotinamide adenine dinucleotide phosphate; NADPH, reduced NADP; OS, overall survival; RFS, relapse-free survival; ROS, reactive oxygen species; SIRT3, sirtuin 3; SPCRP, solid papillary carcinoma with reverse polarity; TET2, tet methylcytosine dioxygenase 2

Key words: isocitrate dehydrogenase 2, hematopoietic diseases, pathological processes, exposure damage, regulatory factors, reactive oxygen species

Contents

1. Introduction

Isocitrate dehydrogenase (IDH) is a key enzyme in the tricarboxylic acid cycle (1) and plays an important role in various metabolic functions and epigenetic cellular processes (2,3). There are three isoenzymes of IDH. The IDH1 and IDH2 genes are located in chromosomes 2q33 and 16q26, respectively (4). At the same time, the IDH3 protein is encoded by the IDH3A, IDH3B and IDH3G genes, which are located in chromosomes 15q25, 20p13 and Xq28 respectively. Structurally, IDH1 and IDH2 proteins are composed of a large domain, a clasp domain and a small domain (5). IDH mutations result in gain-of-function and reduction of α-ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG) (6). Mutated IDH may lead to the development of cancer, especially acute myeloid leukemia (AML) (7).

The expression of IDH2 is affected by exposure factors such as ionizing radiation. IDH2 plays a crucial role in disorders caused by exposure factors (8,9). Therefore, the present study provides an overview of the effect of IDH2 on circulatory system diseases and other system diseases with regard to exposure factors. IDH2 is a mitochondrial enzyme that catalyzes the oxidative decarboxylation of isocitrate to α-KG (10) and protects the body from oxidative stress by converting nicotinamide adenine dinucleotide phosphate ($NADP^+$) to reduced NADP (NADPH) (11). Multiple internal and external factors may contribute to mutations of the IDH2 gene, which may lead to the loss of enzyme activity or obtaining new enzymatic functions (change-of-function) (12). The mutant IDH2 consumes a-KG and NADPH, and produces 2-HG and $NADP^+$ (12) (Fig. 1). Mutations in the IDH2 potein often occur in arginine residues R140 and R172, and are closely associated with the development and progression of AML and glioma (13). Moreover, one study has revealed the effect of wild-type IDH2 on the molecular mechanism of Epstein Barr virus-mediated disease. EBV can cause nasopharyngeal carcinoma in humans, and wild-type IDH2 promotes the survival of nasopharyngeal carcinoma cells (14). Details on the different functions of IDH2 are expounded in the following sections.

2. IDH2 mutations that result in 2-HG accumulation promote the development of hematopoietic diseases

Over past decades, studies have shown that IDH2 is associated with hematological tumorigenesis or disorders, including AML, myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML). The frequencies of IDH2 mutations in diseases of the hematopoietic system, such as AML (15-17), MDS (18,19) and chronic mononuclear leukemia, are 8.0-19, 4-4.6 and 7.8-8.8%, respectively (18,20). Although the frequency of diseases with an IDH2 gene mutation is low, it is crucial to understand the association between IDH2 mutations and disease occurrence. Therefore, the following sections will review the role of IDH2 in various physiological or pathological processes.

Obstructed hematopoietic differentiation caused by IDH2 gene mutations triggers development of hematopoietic neoplasms. IDH2 gene mutations contribute to hematopoietic neoplasms, such as AML and CMML (21,22). AML is a hazardous, enervating and invasive disease with a poor prognosis (23,24). IDH2 and PHD finger protein 6 mutations exert synergistic effects on leukemia formation through excessive production of 2-HG and damage to DNA repair (25). The mutated IDH2 enzyme exhibits gain-of-function activity and catalyzes the conversion of α-KG to 2-HG, which is involved in the pathogenesis of AML (26,27). The 2-HG metabolite is oncogenic and closely associated with the hypermethylation of DNA and histones, which alters the expression of different mRNAs and hematopoietic cell differentiation (28,29). IDH2 gene mutations are crucial for the maintenance of AML progenitor cells, but these mutations may not be the key preliminary step for AML development (30,31). Therefore, further studies are needed to confirm the role of IDH2 mutations in the occurrence of AML. IDH2-mutated cells have significantly increased sensitivity to IL-1β signaling, which may be a potential therapeutic target (32). Furthermore, there are drugs in various stages of clinical development for the treatment of AML with mutated IDH2 proteins, such as AG-221 (enasidenib) (33), AGI-6780 (34), CP-17 (34), TQ05310 (35) and AG-881 (36). AG-221 is an oral, valid, selective inhibitor of mutated IDH2 that has been approved by the US Food and Drug Administration for the treatment of relapsed or refractory leukemia with IDH2 gene mutations. AG-221 binds to the IDH2 dimer interface and blocks the production and accumulation of 2-HG, thereby allowing hematopoietic cells to differentiate from terminal or ancestral mutant clones (37,38). For patients who are unable to benefit from treatment with AG-221 alone, the addition of all-trans-retinoic acid may enhance the response rate of AG-221 therapy (39). Additionally, AG-221 in combination with azacitidine is more effective than azacitidine alone, and is a tolerated and effective treatment option for relapsed or refractory AML that promotes cell differentiation and overall response rates (33,40). There are usually no clinical signs of concurrent infection or clinical features of IDH inhibitor-associated differentiation syndrome, which is characterized by dyspnea, hypoxia, fluid retention and weight gain (41). AG-221 was found to exhibit a poor inhibitory effect on the $IDH2^{R140Q}$ mutation. However, AGI-6780, a preclinical inhibitor, is a selective inhibitor of the $IDH2^{R140Q}$ protein and may be an effective targeted drug therapy for this mutation (34,42,43). In addition, SH1573 is a potential inhibitor of $IDH2^{R140Q}$, and has been demonstrated to be novel, safe and effective, and is currently in clinical trials (44). Furthermore, CP-17 acts as a potent inhibitor of the $IDH2^{R140Q}$ mutant and may be a lead compound for developing drugs against AML (34). Furthermore, TQ05310 showed selective specificity that targeted both $IDH2^{R140Q}$ and $IDH2^{R172K}$ mutant enzymes but had no effect on wild-type IDH or mutated IDH1 (35). AG-881 has lower specificity than the aforementioned drugs and may be useful as an inhibitor of IDH1 and IDH2 mutations for treating associated diseases (37). It is important to note that prognosis can be judged according to the IDH2 mutation site and whether other genes are mutated (2). Moreover, it has been reported that an IDH2 mutation is a marker for poor prognosis in patients with AML, and the overall survival (OS) time of the patients with wild-type IDH2 was greater than that of patients with an IDH2 mutation (45). However, another study found that patients with $IDH2^{R172K}$ mutations have improved relapse-free survival (RFS) and OS times compared with patients with the wild-type (46). Therefore, this topic remains controversial, and more experimental data are needed to confirm which view is correct. CMML is a myelodysplastic/myeloproliferative neoplasm. IDH2 can be used as an indicator of poor prognosis in CMML patients to a lesser extent. One study indicated that patients with IDH2 mutations in CMML had inferior OS rates than wild-type IDH2 patients (17,47).

IDH2 mutations promote the progression of other diseases in the hematopoietic system. IDH2 status not only plays an important role in hematopoietic neoplasms, but also regulates the development of other diseases in the hematopoietic system. Previous studies have discovered that a small number of patients with MDS have IDH2 mutations. The most common IDH2 mutant subtype in MDS is $IDH2^{R140Q}$, and as aforementioned, this mutation results in enzymatic gain-of-function and

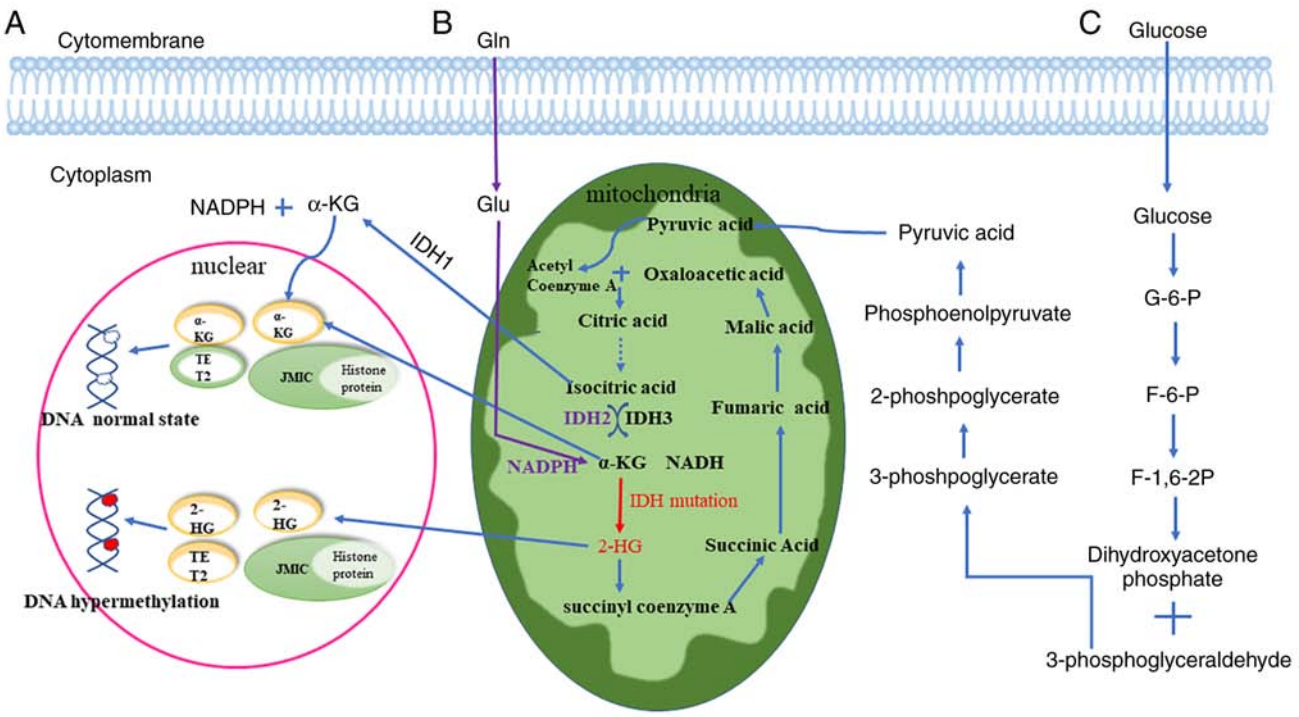

Figure 1. IDH family participates in metabolic processes and epigenetic regulation. (A) α-KG and 2-HG are involved in epigenetic modification. (B) Tricarboxylic acid cycle in the mitochondria. The isocitric acid turns into α-KG via the IDH enzyme family. The IDH enzyme family catalyze the oxidative decarboxylation of isocitrate and therefore play key roles in the Krebs cycle. (C) Glycolysis of glucose in the cytoplasm. G-6-P, glucose-6-phophate; F-6-P, fructose-6-phosphate; F-1,6-2P, 1,6-fructose-diphosphate; α-KG, α-ketoglutarate; 2-HG, 2-hydroxyglutarate; IDH, isocitrate dehydrogenase; Gln, Glutamine; Glu, glutamic acid; NADH, nicotinamide adenine dinucleotide; Jmjc, jumonji C.

inhibition of hemopoietic cell differentiation (48,49). The IDH2 mutation rate in patients with advanced MDS is higher than in those with early MDS (14). Mutations in IDH1 and IDH2 are mutually exclusive (50). Similarly, analysis of patients with MDS showed IDH2 and tet methylcytosine dioxygenase 2 (TET2) gene mutations do not exist simultaneously (51). IDH2 mutations may be involved in the development but not the progression of MDS (52). Moreover, high 2-HG serum levels predict the presence of IDH2 mutations; thus, mutated IDH2 proteins can be used as targets for pre-transplantation and post-transplantation treatment of MDS (53,54). For effective treatment of MDS with IDH2 gene mutations, the mutated protein can be specifically targeted (19). For example, AG-221 is an effective drug for the treatment of MDS with IDH2 mutations, including use in those patients for whom the use of hypomethylating agents has been unsatisfactory (55). There is a poor OS time among patients with MDS and IDH2 mutations under low-risk stratification in the International Prognostic Scoring System (53,56). In summary, IDH2 plays an extremely important role in the generation and progression of some diseases of the hematopoietic system, and can be used as a molecular marker and target for therapy.

3. Associations between IDH2 gene status and other pathological processes

IDH2 is closely associated with therapeutic effectiveness and sensitivity. IDH2 is not only associated with blood circulation disorders, but also with other diseases, such as glioma (57), non-small cell lung cancer (58), solid papillary carcinoma with reverse polarity (SPCRP) (59), angioimmunoblastic T-cell lymphoma (AITL) (60), high-grade chondrosarcoma (61) and undifferentiated sinus carcinoma (62).

IDH2 gene mutations participate in nervous system diseases, especially in gliomas. IDH2 mutations play an important role in some diseases of the nervous system, such as gliomas and 2-hydroxyglutaric aciduria. Studies have shown that IDH2 mutations are a driving factor in gliomas, especially in low-grade gliomas and glioblastomas (57,63). Glioma subtypes with IDH2 gene mutations have unique clinical characteristics. For instance, IDH2 mutations are more common in younger individuals and are more likely to occur in low-risk surgical areas (64). Furthermore, IDH2 can be used as a biomarker with diagnostic, prognostic and predictive implications (65,66). In gliomas, IDH2 mutations were found to be mutually exclusive with IDH1, phosphatase and tensin homolog, cellular tumor antigen p53 and α-thalassemia retardation syndrome X-linked mutations (63). Injecting mutated IDH2 into glioma mice accelerated tumor growth and increased mortality rate compared with that in mice with wild-type IDH2 (67). Moreover, IDH2 mutations are significantly correlated with the incidence of preoperative glioma-related epilepsy, and affect the surgical resectability of gliomas (68,69). IDH2 mutations may also trigger the development of 2-hydroxyglutaric aciduria and Parkinson's disease (70,71).

Tumor cell growth is promoted by wild-type IDH2. In addition to playing an important role in the progression of neurological diseases, IDH2 gene status promotes the development of

certain respiratory diseases. Studies have shown that the IDH2 protein plays a role in specific lung cancer types; for example, IDH2 plays an important role in non-small cell lung cancer (58). The expression level of IDH2 in the serum of patients with non-small cell lung cancer is higher than that of the normal population, and after treatment, the expression of serum IDH2 in patients with non-small cell lung cancer decreases (58). Notably, the IDH2 rs11540478 genetic variant represents a novel susceptibility locus for lung cancer; it can change the level of IDH2 protein, and affect cancer cell viability and disease evolution (72). Compared with patients with lung cancer, healthy individuals have lower levels of IDH2 mRNA in peripheral blood lymphocytes (66). Wild-type IDH2 promotes the development of lung cancer, and an increased level of IDH2 protein is a characteristic of poor survival (73). Overall, IDH2 may represent a target for lung cancer treatment. Furthermore, IDH2 is important for the progression of lung injury. IDH2 has different effects depending on the cause of the lung injury. IDH2 can reduce acrolein-induced lung injury by providing NADPH (74), and as a provider of the pro-inflammatory metabolite α-KG, IDH2 is indirectly involved in lipopolysaccharide-induced acute lung injury. Therefore, targeting the IDH2 enzyme may be a treatment strategy for systemic inflammatory response syndrome (75).

Status of the IDH2 gene affects peripheral T-cell lymphoma. AITL is a subtype of peripheral T-cell lymphoma that is affected by IDH2 gene status. It has been reported that IDH2 expression is significantly upregulated in patients with myeloproliferative neoplasia (MPN)-AITL compared with that in AITL patients without MPN (76). Meanwhile, it has also been reported that mutated IDH2 and TET2 proteins usually occur together in AITL (60,77). In one study, AITL with the $IDH2^{R172}$ mutation displayed a limited gene expression profile that correlated with cellular differentiation, and genes associated with interleukin-12 stimulation were significantly enriched (78). Moreover, an AITL case with mutated IDH2 protein presented with high intracellular levels of 2-HG without an increase in circulating 2-HG. This case suggests that levels of circulating 2-HG may not accurately reflect the presence of IDH2 gene mutations (79). In 20-30% of patients with AITL, IDH2 has diagnostic value and is a potential therapeutic target. Next-generation sequencing technology and allele-specific quantitative polymerase chain reaction show good sensitivity for the detection and diagnosis of IDH2 mutations (80). As expected, compared with the TET2 gene mutation alone, TET2/IDH2 co-mutations conferred longer progression-free survival times to affected patients (81).

Course of other diseases is also affected by IDH2 gene status. IDH2 status is important in other diseases, such as SPCRP, prostate and colon cancer. A previous clinical study determined that 77% of SPCRP cases had an IDH2 hot spot mutation at amino acid site 172 (59). One study indicated that the $IDH2^{R172}$ mutation was highly specific for SPCRP in various subtypes of breast cancer, and that it may be a suitable diagnostic marker for SPCRP and guide effective treatment (82). Furthermore, high expression levels of IDH2 mRNA or protein were associated with a poor outcome in patients with invasive breast cancer (83). Enzymatic malfunction of IDH2 in prostate cancer cells disrupted oxidative bioenergetics, enhanced reactive oxygen species (ROS) generation and increased mitochondrial dynamics (84). Frequent IDH2 gene mutations have recently found in central chondrosarcomas, which resulted in longer RFS and metastasis-free survival times in high-grade chondrosarcomas; however, no association with OS was observed (61). Undifferentiated sinus carcinoma is an infrequent, aggressive, highly malignant tumor with finite therapy choices (85,86), and women with this disease have a higher frequency of IDH2 mutations compared with men with the disease (87). IDH2 mutated undifferentiated sinus carcinoma subtypes have high levels of DNA methylation and a poor prognosis (62). As a prime component in anti-oxidative damage, wild-type IDH2 protects cochlear hair cells from ROS and prevents age-related hearing loss by providing NADPH (88,89). Moreover, IDH2 is vital for conditions that develop from ROS exposure or mechanical damage (90). For example, IDH2 has a protective effect against ultraviolet B radiation-induced skin damage and is involved in skin wound healing (90,91). Downregulation of IDH2 protein is likely one of the mechanisms underlying 5-hydroxymethylcytosine loss in melanoma (92). Studies have shown that IDH2 knockout can inhibit the growth of colon cancer cell lines. Thus, the IDH2 enzyme has an important impact on the generation and progression of colon carcinoma (93,94). IDH2 may be a target to treat skin pigmentation, as IDH2 deficiency can cause skin pigmentation (95). Additionally, IDH2 may be a therapeutic target for adipose inflammation (96,97). In summary, IDH2 gene status drives the process of multiple diseases and may serve as a biomarker and/or therapeutic target (Table I).

4. IDH2 level is affected by exposure to environmental hazards

IDH2 protects cells from radiation damage by producing NADPH. IDH2 not only greatly contributes to the progression and treatment of diseases, but it is also involved in the maintenance of cellular metabolism under conditions of environmentally induced damage. IDH2 can protect cells from damage caused by excessive ROS production after cells are exposed to ionizing radiation (98). ROS are natural products of mitochondrial metabolism and can trigger oxidative damage (99). The protective effect of IDH2 on cells is based on the reduction of $NADP^+$ to NADPH, which is a precondition for some cellular defense systems to reduce oxidative damage (100,101). Imbalance between mitochondrial oxidation and reduction reactions causes cell death in organisms exposed to ionizing radiation. When organisms are exposed to ionizing radiation, the level of ROS increases and the NADPH regulated by IDH2 to the antioxidant system decreases (102,103). Wild-type IDH2 protects cells against γ-irradiation by maintaining NADPH levels that buffer against radiation-induced ROS and protect cells from apoptosis. The latest studies and clinical data from the European Organization for Research on Treatment of Cancer trial have verified that gliomas with IDH2 gene mutations are extremely sensitive to radiotherapy (104-106). Furthermore, IDH2 not only protects the cells from ionizing radiation, but also protects the cells from non-ionizing radiation. Under the non-ionizing radiation environment, IDH2 has a protective effect on ultraviolet B-induced skin damage (90).

Table I. Associations between status of IDH2 and multiple diseases.

A, Mutation

Disease	Effect of pathological progression	Prognosis	(Refs.)
AML	Maintain tumor cells and promote disease progression	Negative prognostic marker	(30,45)
CMML		Unfavorable molecular prognostic factor	(17,47)
MDS	Participating in what happens does not promote progress	Poor	(48,53)
Glioma	Driving factors	Longer OS and PFS times	(66,67)
AITL	Promote disease progression	Longer PFS time	(84)
SPCRP	Driving factors	Patients with high expression of IDH2 have poor outcome in IBC	(59,83)
High-grade chondrosarcoma		Longer relapse- and metastasis-free survival times	(61)
Undifferentiated sinus carcinoma		Higher survival rate	(62,87)

B, Upregulated expression of wild-type IDH2

Disease	Effect of pathological progression	Prognosis	(Refs.)
Lung cancer	Contribute to cancer cell growth and survival	Poor	(58,73)

IDH2, isocitrate dehydrogenase 2; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; AITL, angioimmunoblastic T-cell lymphoma; SPCRP, solid papillary carcinoma with reverse polarity; OS, overall survival; PFS, progression-free survival.

IDH2 activity is regulated by binding to heavy metal ions and toxic substances. Environmental heavy metals affect the enzymatic activity of IDH2. When organisms are exposed to heavy metals, such as cadmium (Cd^{2+}) (107), $CoCl_2$ (108), mercury (109) or copper (8), the expression of IDH2 may be altered. Cd^{2+} ions have a dual effect on cells. Cd^{2+} activates IDH2, and activated IDH2 provides NADPH for cellular defense, as aforementioned. However, Cd^{2+} ions have a high affinity for thiols and contribute to the combination between Cd^{2+} ions and cysteine residues, which trigger IDH2 inactivation. Therefore, cells exposed to cadmium are prone to apoptosis (107,110). Removing cadmium from the environment with microorganisms is difficult due to its toxicity. The yeast *Pichia kudriavzevii* has been used as a model organism for cadmium removal, and acid stress can reduce the toxicity of Cd^{2+} and upregulate genes associated with ATP synthesis, such as IDH2 (111). $CoCl_2$ can indirectly affect IDH2 expression. Hypoxia was induced by $CoCl_2$ treatment increasing the expression of IDH2 in breast cancer cells after radiation (108). Jejunal epithelial cells induce mitochondrial dysfunction and mitosis through the Mitomir-1285-IDH2 axis during copper exposure Mitomir-1285 aggravates copper-induced mitochondrial dysfunction by inhibiting IDH2 expression (8) (Fig. 2). Exposure to arsenic in pregnant rats indirectly induces anxiety-like behavior in adult offspring through downregulation of IDH2 expression in the fetal brain (9). Moreover, some lower animals, such as bivalves and corals, may also be affected by heavy metals, resulting in a change in IDH2 activity. For example, bivalves exposed to mercury alone showed a reduction in IDH2 activity and a subsequent alteration in cellular energy production (109). When corals were exposed to copper, IDH2 activity was inhibited, and aerobic and oxidative metabolism was reduced (112) (Fig. 2) (Table II).

5. Regulation of IDH2 level is a multi-factor and multi-pathway process

IDH2 is involved in protecting cells from oxidative stress-induced by ROS (113). Deficiency causes abnormal mitochondrial function, which increases the production of ROS, promotes cell senescence by inducing cell-cycle arrest, impairs cell function and stimulates development of age-related diseases (89,114). As IDH2 makes a significant contribution to homeostasis and cellular differentiation, the following sections will discuss the factors and associated mechanisms that regulate IDH2 expression and activity.

Sirtuin3 (SIRT3) expression is positively associated with IDH2 activity. IDH2 is regulated by SIRT3 and other factors. SIRT3 is regulated by acetylation, which is a post-translational modification that alters its activity (115,116). IDH2 activity is increased significantly after deacetylation by SIRT3, which is

Table II. Effect of different exposure environments on IDH2.

Exposure environment	Related effect	Model	(Refs.)
Ionizing radiation			
γ-ray	IDH2 protects cells from oxidative stress	Mouse, NIH3T3 cells	(100)
	IDH2 knockdown triggers radiation-reduced metabolism disorder in mitochondria	Esophageal squamous cell carcinomacell lines	(98)
	IDH2 expression is negatively correlated with radiation therapy sensitivity	Mouse	(102)
Non-ionizing radiation			
UVB	UVB-induced apoptosis and inflammation in the skin of IDH2-deficient mice	Mouse	(90)
Heavy metals and toxic substances			
Cd^{2+}	Dual effect: Activates IDH2 by providing two ions, and inactivates IDH2 via high affinity for thiols	*Escherichia coli*	(107,110)
$CoCl_2$	Can enhance IDH2 expression	Breast cell line MCF-7	(108)
Arsenic	Downregulation of IDH2 expression	Pregnant rats	(9)
Mercury	Suppresses IDH2 expression	Bivalves	(109)
Copper	Suppresses IDH2 expression	Coral	(112)

IDH2, isocitrate dehydrogenase 2; UVB, ultra violet B; Cd^{2+}, cadmium.

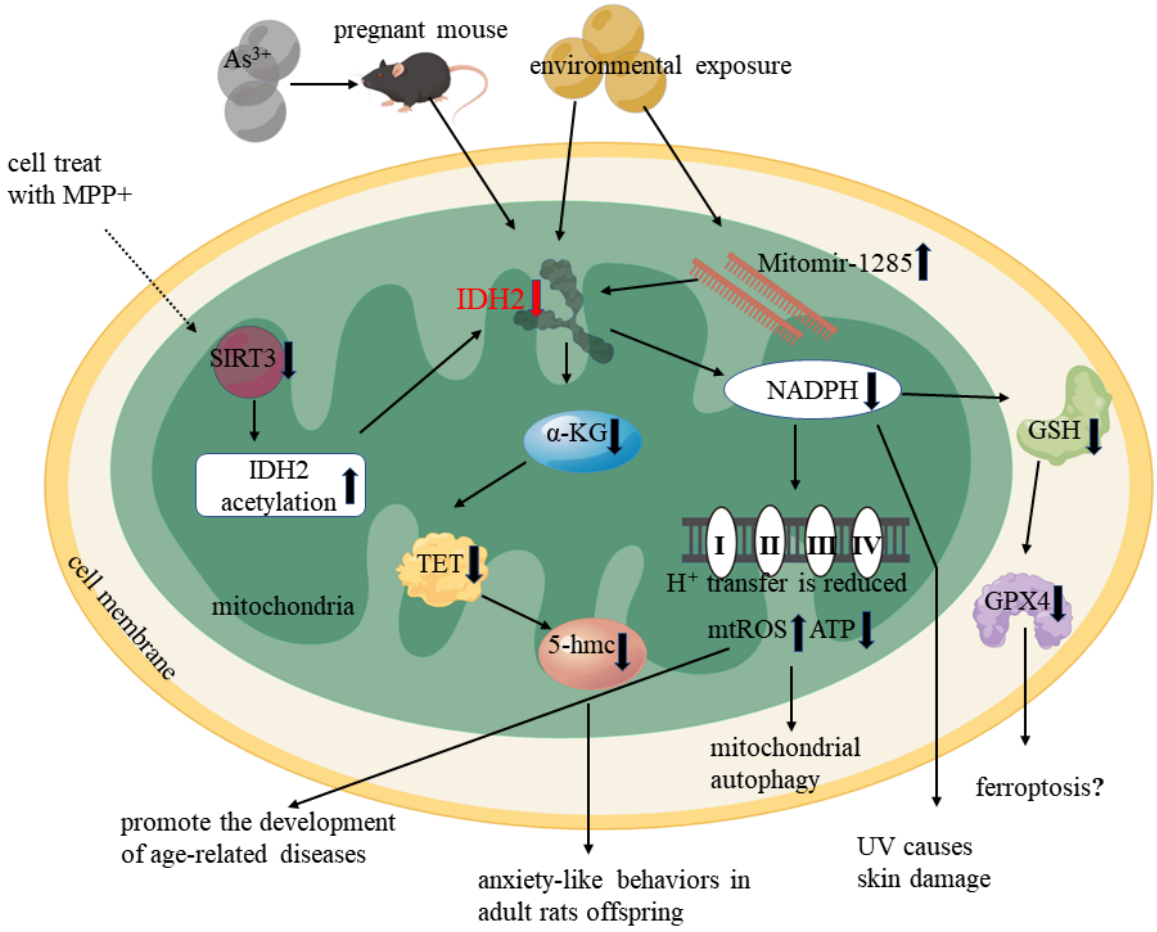

Figure 2. Pathway diagram for the regulation of IDH2. Internal or external factors (such as radiation and metals in the environment) cause changes in the expression or activity of IDH2, resulting in skin damage and mitochondrial autophagy, among others. MPP^+, methyl-4-phenylpyridinium; TET, methylcytosine dioxygenase; α-KG, α-ketoglutarate; 5-hmc, 5-hydroxymethylcytosine; mtROS, mitochondria reactive oxygen species; MDA, malondialdehyde; As^{3+}, arsenic; UV, ultraviolet; GPX4, glutathione peroxidase 4; GSH, glutathione; SIRT3, sirtuin 3; IDH2, isocitrate dehydrogenase 2.

a deacetylase in mitochondria. A decrease in SIRT3 protein reduces IDH2 enzymatic activity by decreasing IDH2 dimer formation (117,118) (Fig. 2). For example, in one study, during therapy for multiple myeloma, the combination of carfilzomib with SIRT3 inhibitors decreased IDH2 activity and increased multiple myeloma cell death (118). Overexpression of nicotinamide mononucleotide adenylate transferase 3 in bone marrow mesenchymal stem cells enhanced the ability of specific antioxidant stress by enhancing SIRT3 activity and decreasing IDH2 acetylation level (119).

Other moderating factors that regulate levels and activity of IDH2. To avoid damage caused by oxidative stress, the antioxidant activity of IDH2 can be enhanced by SUMOylation (120). A previous study showed that the activity of IDH2 is affected by post-translational modification. Under oxidative stress, IDH2 ubiquitination deficient cells had more apoptosis than normal cells, suggesting that ubiquitination is an important means of regulating IDH2 activity (120). Furthermore, $IDH2^{R140Q}$ and cytoplasmic nucleophosmin mutation increase myeloid ecotropic viral integration site 1 and homeobox A9 gene expression, respectively, which activates the hypoxia pathway in AML cells (121). Cells expressing the mutant IDH2 protein are deficient in their capacity for reductive carboxylation and the ability to produce acetyl-CoA may be impaired under hypoxic conditions. Acetyl-CoA is involved in certain metabolic processes in the body, such as cholesterol synthesis, fatty acid generation and glucose metabolism (122). In addition, decreased IDH2 expression may promote ferroptosis through the coordination of erastin (ferroptosis inhibitor) with the NADPH-glutathione-glutathione peroxidase 4 (GPX4) axis (Fig. 2) (123). Taken together, these factors provide new insight into the treatment of diseases involving the IDH2 gene.

6. Prospects

The present review summarizes the existing knowledge relating to various aspects of IDH2 expression and activity. IDH2 and its associated diseases, mechanisms of action and alterations after exposure to radiation and heavy metals are described. A number of environmental exposure factors can inhibit IDH2 expression or activity, indirectly leading to decreased GPX4 expression, which may lead to ferroptosis, but the specific mechanism is not clear. Further research may provide therapeutic methods for some diseases so that patients can obtain more accurate and effective treatment plans. In addition, it is possible to find other factors that regulate normal levels of IDH2 and maintain homeostasis in response to radiation exposure, a strategy that may have great application value. Furthermore, IDH2 is promising as a marker of environmental exposure for circulatory diseases. On the basis of the important role of IDH2 in blood circulatory system disorders, it is feasible to recommend IDH2 as a novel biomarker for environmental exposure in blood circulatory system disorders both theoretically and practically.

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Availability of data and materials

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Authors' contributions

YQG and SW completed the writing and proofreading of the manuscript. YYW, YLC, and JC revised the manuscirpt critically for intellectual content and created the figures and tables. YQY, XL, HXY, and HQ made corrections to the original manuscript and also performed literature searches. LY was involved in the conception, directed the writing of the article, and made partial revisions. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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