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Function, drug resistance and prognostic effect of AKR1C2 in human cancer

Minireview

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Aldo-keto reductases (ARKs), a group of reductases that rely on nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) to catalyze carbonyl, are widely found in various organisms, which play an important role in the physiological and pathological processes of human. Aldo-keto reductase family 1 member C2 (AKR1C2) as a member of the human ARKs family, can regulate steroid hormones and is abnormally expressed in many cancers. According to whether the tumor can be affected by hormones, we divide malignancies into hormone-dependent and hormone-independent types. Studies have shown that AKR1C2 is involved in regulating tumor invasion, migration, and other malignant phenotypes, eliminating reactive oxygen species (ROS), promoting chemotherapy resistance of tumor cells, and has prognostic value in some cancers. Here, we focus on the role and clinical significance of AKR1C2 in different types of tumors.

Key words: AKR1C2; cancer; steroid hormone metabolism; drug resistance

Aldo-keto reductases (AKRs) are members of the oxidoreductases superfamily and can be observed in prokaryotes and eukaryotes [1–4]. According to the 40% amino acid identity level, AKRs are divided into 16 families [5, 6]. At present, the AKRs family has been found to have 191 members [5]. The molecular weight of the proteins encoded by these genes is mostly between 35–40 kDa, mainly in the form of monomers [7, 8]. Humans have 15 kinds of AKRs [9], which can metabolize aldehydes, ketones, steroids, and other substances by using NAD(P)(H) [1, 2, 4]. Aldo-keto reductase family 1 member C2 (AKR1C2) is a member of the AKR1 family, which is located on human chromosome 10, with a total of 9 exons and 10 transcripts [9–11]. The protein encoded by this gene is 37 kDa, which is mainly distributed in the cytoplasm of cells and is closely related to AKR1C1, AKR1C3, and AKR1C4 (Figures 1A, 1B) [12, 13]. High protein expression of AKR1C2 can be detected in human liver, stomach, and bladder tissue [14]. However, it cannot be detected in some tissues such as placenta, spleen, bone marrow, and lymph nodes [14].

It is suggested that AKR1C2 is involved in the formation of steroid hormone biosynthesis, DNA adducts, and reactive oxygen species (ROS), which are closely related to tumor formation and development [15–20]. 5α-dihydrotestosterone (DHT) and progesterone (P4) are both steroid hormones. DHT can be metabolized by AKR1C2 to 5α-androstane-3α,17β-diol (3α-diol) (weak androgen) (Figure 2A) [15, 16, 21, 22]. AKR1C2 also metabolizes P4 into other products (Figure 2B) [23–25]. Changes in steroid hormone levels can lead to canceration of hormone-dependent tissues such as the prostate and breast. The expression of AKR1C2 was increased when cells were exposed to carcinogens such as polycyclic aromatic hydrocarbons (PAHs), benzo[a]pyrene, or 1-nitropyrene, which can metabolize these toxic substances into active substances that can form adducts with DNA [17, 18]. If not repaired in time, the formation of DNA adducts will damage DNA and induce cell cancerization [26, 27]. AKR1C2 can reduce the ROS level in cancer cells to tolerate oxidative stress and drug stimulation, ultimately reducing death [18–20, 28]. In addition, AKR1C2 is also abnormally

expressed in many tumors [29–31]. Therefore, in this article, we reviewed the role of AKR1C2 in different tumors.

Antioxidant responsive element of AKR1C2

Kelch-like ECH-associated protein 1 (Keap1)-Nuclear factor erythroid 2-related factor 2 (Nrf2)- Antioxidant responsive element (ARE) is a classical oxidative stress signaling pathway. Keap1 is the substrate adaptor protein of Cullin 3 (Cul3) dependent E3 ubiquitin ligase complex [32, 33]. Under normal conditions, two Keap1 proteins can bind to one Nrf2, bridge it to Cul3, and promote the ubiquitination of Nrf2. However, when cells are exposed to abnormal environments such as radiation, drugs, and poisons, they are in a state of stress, resulting in increased ROS levels [34–36]. The cysteine residues in Keap1 are modified to change the conformation of the Cul3/Keap1/Nrf2 complex. Nrf2 is no longer ubiquitinated but enters the nucleus. After heterodimerization with small Maf proteins (sMAFs), they combine with the AREs of Nrf2 target genes to promote the transcription and translation of downstream genes. The redox balance of cells is restored to cope with the damage caused by stress. Keap1-Nrf2-ARE is the key mechanism of tumor therapeutic resistance [37, 38]. Many human AKRs have ARE, and there is an ARE upstream of the AKR1C2 promoter, which can be regulated by Nrf2 (Figure 3) [39–42]. Phase II Inducer can promote the combination of NRF2 and ARE on AKR1C2 promoters in HepG2 cells. In HT-22 hippocampal cells, isosilybin and tert-butylhydroquinone upregulated AKR1C2 through the activation of the Nrf2/ARE pathway to alleviate oxidative stress damage induced by Aβ25-35 [43]. Panaxytriol could induce the combination of Nrf2 and AKR1C2 ARE by stimulating IMR-32 cells [44]. High expression of Nrf2 and AKR1C2 was observed in oxaliplatin-resistant gastric cancer cells [45]. After the downregulation of Nrf2, the expression of AKR1C2 was reduced, and the drug sensitivity of cells was restored. MSU38225, an Nrf2 pathway inhibitor, significantly inhibited AKR1C2 and upregulated ROS in lung cancer cells, enhancing the sensitivity of cells to chemotherapy drugs [46]. In short, when the body is under oxidative stress, the Nrf2/ARE pathway is easily activated to increase the expression of AKR1C2, which will make the body more tolerant to the damage caused by the stimulus.

The role of AKR1C2 in cancer

Hormone-dependent malignancies.

Prostate cancer. Prostate cancer is the most common malignant tumor among men in the world, with the fifth mortality rate, which threatens the life and health of men [47]. The incidence of prostate cancer is closely related to family genetic history, age, inflammation, high insulin diet, and so on[48–50].

Androgen is closely related to the occurrence and development of prostate cancer, and the reduction of androgen level, such as castration surgery or endocrine therapy, are critical treatment methods [51]. DHT, the main component of androgen, can be restored to 3α-diol by AKR1C2 (Figure 2A) [52]. Overexpression of AKR1C2 in monkey COS-1 kidney cells (an AKR1C null environment) and PC-3 cells with negative androgen receptor (AR) catalyzed the inactivation of DHT [53, 54]. The PC-3 cells with different

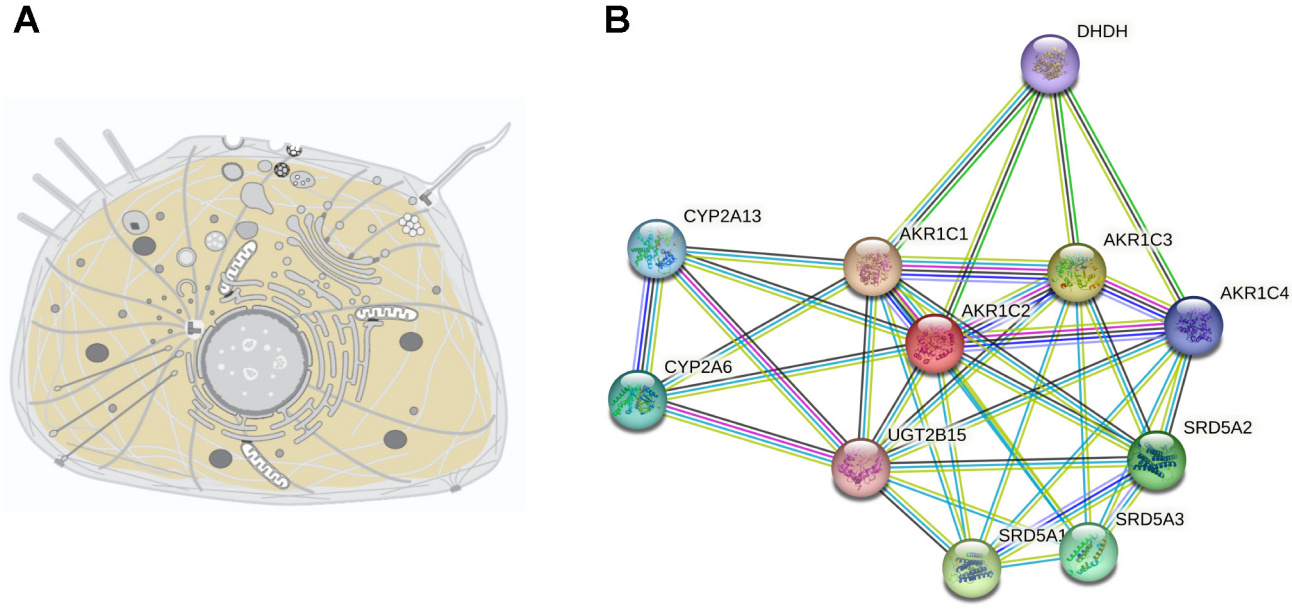

Figure 1. A) Distribution of AKR1C2 in cells, mainly in the cytoplasm. Source Uniprot [12]. B) Protein network interacting with AKR1C2. Source String [13].

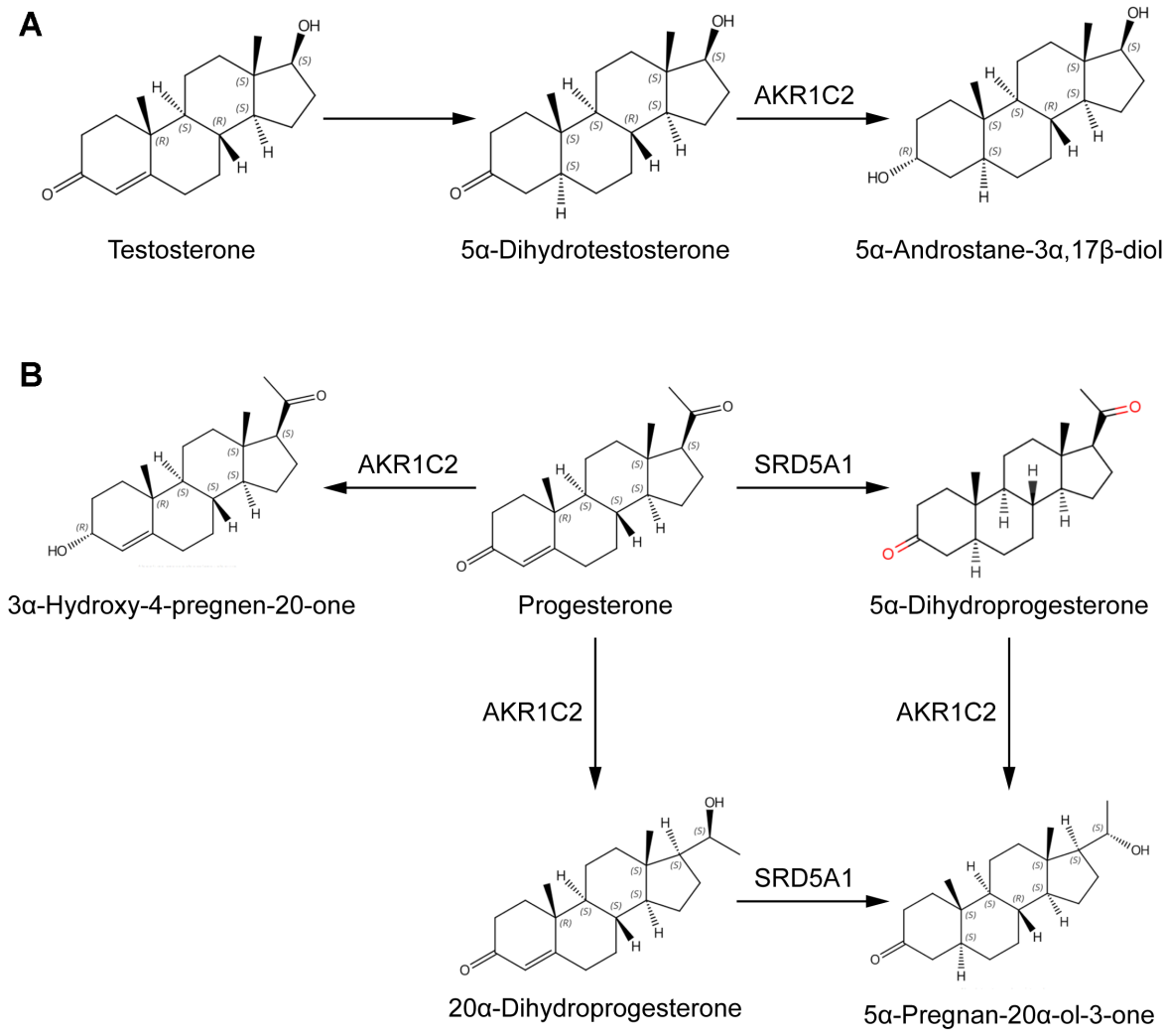

Figure 2. AKR1C2 and SRD5A1 in A) androgen and B) progesterone metabolism.

AKR1C2 expression levels were incubated with a medium of 3.4 nM DHT concentration [15]. With the increase of AKR1C2 level, the amount of 3α-diol in the culture medium and cells increased gradually. Curcumin could inhibit the growth of prostate cancer and promote its apoptosis in a dose-dependent manner, induce the expression of AKR1C2, and gradually reduce the levels of testosterone (T) and DHT in LNCaP, the AR-positive prostate cancer cells [55]. Similarly, the use of the extract of neem leaves also promoted the protein level of AKR1C2 and inhibited the growth of prostate cancer *in vivo* and *in vitro* [56, 57]. The researchers found that AKR1C2 was relatively absent in most prostate cancer patients compared with benign prostates, and the metabolic pathway from DHT to 3α-diol was significantly blocked [21]. *In vitro* experiments confirmed that increasing the expression of AKR1C2 can reduce the proliferation stimulated by DHT in prostate cancer cells. In order to understand the expression of androgen metabolizing enzymes in benign and malignant prostate tissues, Khvostova et al. compared 12 cases of prostate cancer and paired normal tissues [29]. They found that AKR1C2 was significantly lower expressed in prostate cancer tissues. Through a meta-analysis of multiple prostate cancer data sets with large sample size, Zhang et al. also observed the downregulated expression of AKR1C2 in primary prostate cancer [58]. Combined with the results of several studies, it is not difficult to find that AKR1C2 does have the function of metabolizing DHT in prostate cancer. Promoting the expression of AKR1C2 in the androgen metabolism pathway may inhibit the progression of prostate cancer.

However, in some prostate cancer studies, AKR1C2 can promote the occurrence and development of prostate cancer independently of the androgen signaling pathway. Adriamycin belongs to the anthracycline drugs, which kill tumor

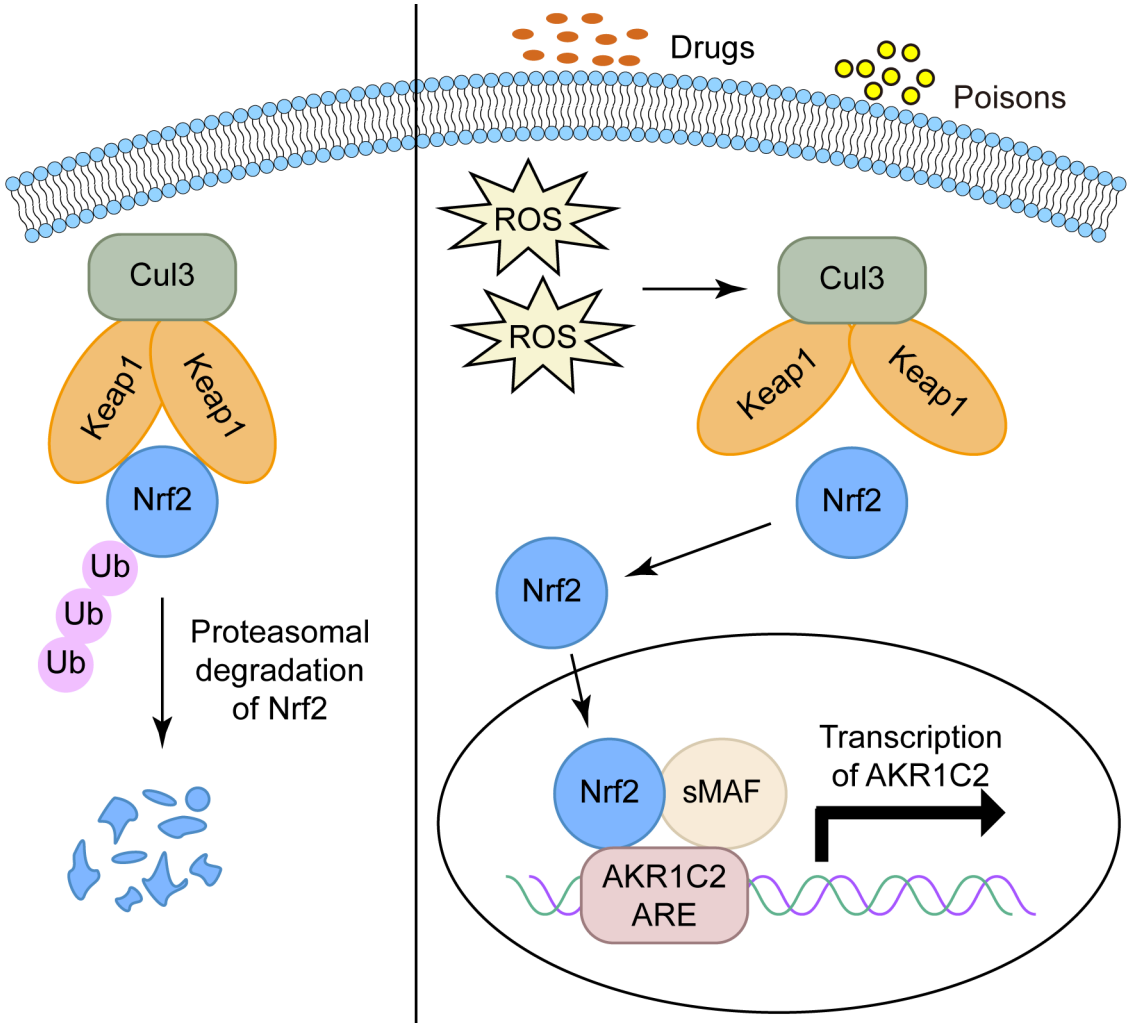

Figure 3. Regulation mechanism of Keap1-Nrf2-AKR1C2's ARE. Under normal conditions, Keap1 protein can bind Nrf2 and promote Nrf2 ubiquitination. When cells receive stimulation, Keap1 protein no longer binds Nrf2, and Nrf2 enters the nucleus and binds with the ARE element of AKR1C2 to promote the transcription of AKR1C2.

cells by inducing DNA damage [59]. Cisplatin is a common anticancer drug that plays an anticancer role by inhibiting DNA replication [60]. In the medium without androgen, the high expression of AKR1C2 not only promoted the proliferation of prostate cancer cells but also enhanced the resistance of cells to adriamycin and cisplatin [61, 62]. In Huang et al.'s study, the expression level of AKR1C2 in prostate cancer tissues was not only higher than that in benign tissues, but also positively correlated with Gleason score, smoking, and AR expression [62]. Among prostate cancer, the prognosis of type 2 diabetes patients was inferior to that of patients without diabetes [63, 64]. AKRs, as NAD(P)(H) dependent oxidoreductases, also participate in carbohydrate metabolism [65, 66]. A high glucose environment stimulated the expression of AKR1C2 in prostate cancer tissues and cells, with a significant positive association in carcinogenic pathways such as HIF1α, NFκB, which might be an important reason for the worse prognosis of diabetic prostate cancer patients [67].

Female breast cancer. Female breast cancer is the malignant tumor with the highest incidence rate in most countries [47]. Although the mortality of breast cancer has decreased in recent years, its incidence rate is increasing, one of the main reasons is the positive hormone receptor [68, 69]. Hormone-dependent breast cancer is the most common subtype of breast cancer, treatments targeting estrogen and P4 can be a benefit to these patients.

The P4 metabolites in breast tissue are 5α-dihydroprogesterone (5αP) and progesterone in the carbon-4 position of ring A (4-pregnenes), mainly 3α-hydroxy-4-pregnen-20-one (3αHP), which can promote or inhibit the progression of breast cancer, respectively [70]. The conversion from P4 to 5αP requires 5α-reductase (5αR), which

efficiency mainly depends on 5α-reductase type 1 (steroid 5 alpha-reductase 1 (SRD5A1)), while 3α-hydroxysteroid oxidoreductase (3α-HSO) is the enzyme required for the conversion of P4 to 3αHP (Figure 2B) [71, 72]. The activity of 3α-HSO in benign mammary epithelial cells (MCF-10A) and tissues was stronger than that of breast cancer, and 5αR was opposite to 3α-HSO [70, 71]. AKR1C2, also called 3α-HSO3, was a member of 3α-HSO, whose mRNA content in breast tumor cells was significantly lower than that of MCF-10A [71]. The expression of AKR1C2 in breast cancer tumors was significantly lower than that in paired or unpaired tumor-free tissues [30]. On the contrary, the levels of SRD5A1 and SRD5A1/AKR1C2 in tumor tissues were significantly higher than those in normal tissues, suggesting the different distribution of P4 metabolizing enzymes in normal and malignant breast tissues. The low expression of AKR1C1 and AKR1C2 not only reduced the metabolism of P4 but also increased the binding of P4 and P4 receptor (PR) to accelerate the growth of breast cancer cells [73]. Through the tissue microarrays of 504 breast cancer samples, AKR1C2 was positively correlated with age, negative lymph node status, L0 and M0 status in fibroblasts [74]. Similarly, the high expression of AKR1C2 in breast cancer cells was closely related to small tumor size, ductal subtype, and L0 status [74]. Survival analysis suggested that patients with high AKR1C2 levels in fibroblasts or breast cancer tissue had longer disease-free survival (DFS) and overall survival (OS) [74]. To sum up, AKR1C2 can metabolize P4 into 4-pregnenes with the anti-tumor effect. The absence of AKR1C2 will promote the progress of breast cancer. Based on the regulation of AKR1C2 on P4 in breast cancer, targeting AKR1C2 may play an important role in the prevention and hormone treatment of breast cancer.

Endometrial cancer. Endometrial cancer is one of the three major gynecological malignancies, among which endometrioid cancer is the most common pathological type. Endometrioid endometrial carcinoma often originates from long-term exposure to estrogen without P4 [75]. Endogenous or exogenous P4 supplementation can reduce the risk of the disease [76].

Endometrial cancer cells can metabolize P4. AKR1C1-AKR1C3 and SRD5A1 were detected in endometrial cancer cells Ishikawa and HEC-1A [23]. The use of small interfering RNA to silence AKR1C1/AKR1C2 inhibited the 20-ketosteroid reduction of P4 and 5α-pregnanes, while SRD5A1 silencing inhibited the 5α-reduction of P4 (Figure 2B), and the P4 level in the culture medium of two groups were higher than that in the negative control group. Sinreih et al. speculated that AKR1C2 and SRD5A1 played an important role in P4 metabolism. However, since the authors did not knock down AKR1C2 specifically, relevant experiments were needed to confirm the conjecture. It is worth noting that in the comparison between 47 pairs of endometrial cancer and control endometrial tissues, the P4 receptor was significantly downregulated in cancer tissues while AKR1C2 and SRD5A1 showed no significant difference [77]. The cause of malignancy of the endometrium may be the reduction of the antagonistic effect of P4 on estrogen by inhibiting the efficiency of P4 action without affecting P4 metabolism. We consider that AKR1C2 may not affect the endometrial carcinogenesis process, but AKR1C2 alters the P4 metabolism level in endometrial cancer cells. The role of AKR1C2 in endometrial cancer requires expanded patient samples and more in-depth experiments.

Hormone-independent malignancies

Non-small cell lung cancer. Smoking and environmental particles will increase the risk of lung cancer [78–81]. Among all cancers, lung cancer has the highest mortality rate in the world [43]. Non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer. Systemic chemotherapy based on cisplatin is the first-line treatment for NSCLC [82, 83]. Cisplatin resistance is a major obstacle to the prognosis of lung cancer, so it is necessary to find the key factors that can change the sensitivity of cisplatin.

Many studies have shown that the expression of AKR1C2 in lung cancer is closely related to cisplatin resistance. Hung et al. found that overexpression of AKR1C2 in H23 cell lines could significantly improve the resistance to adriamycin, cisplatin, and radiation [84]. Further study found that proinflammatory factors such as IL-6 could induce the expression of AKR1C1/AKR1C2 in H23 cells, and enhance the resistance of cells to cisplatin and doxorubicin at the same time, while wogonin and chrysin could reverse this phenomenon [85]. Conversely, decreasing the expression of AKR1C2 in A549 cells would increase the sensitivity to cisplatin [86]. The clinical results also confirmed this viewpoint. Compared with A549, proteomics showed that AKR1C2 was significantly overexpressed in A549/DDP, a cisplatin-resistant cell line based on A549, suggesting that AKR1C2 might play a role in altering cell drug sensitivity [87]. According to serum detection of NSCLC patients before treatment, the average level of AKR1C2 in patients who were resistant to the treatment was significantly higher than in the treatment-sensitive group. Not surprisingly, AKR1C2 was highly expressed in NSCLC compared to healthy people, and adenocarcinoma was higher than squamous cell carcinoma [31]. Furthermore, high AKR1C2 levels indicated worse TNM staging, which has predictive value in distinguishing healthy people from NSCLC.

4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is a strong carcinogen in tobacco smoke [88]. *In vivo*, it is metabolized into 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and excreted out of the body. As a member of the reductase, AKR1C2 participated in this process. People with AKR1C2 haplotype C-C-A-A-C-C-T-A-A-C-A in block 2 had a significantly increased risk of lung squamous cell carcinoma [89]. The incidence of lung cancer in women has been increasing year by year in many countries but declining in men [90, 91]. Stapelfeld et al. found that ethinylestradiol, drospirenone, and P4 had a stronger inhibitory effect on

AKR1C2, which mediated the reduction of NNK to NNAL than T, would affect the detoxification of NNK *in vivo* [92].

Gastric cancer. Although the incidence of stomach cancer has continued to decline in recent decades, both the incidence and mortality rate of stomach cancer still remains among the top five in the world, and it is far more common in men than women [68, 93, 94]. There are a few reports about AKR1C2 and gastric cancer, most of which are associated with Twist. Twist induces epithelial-mesenchymal transition (EMT) in gastric cancer cells [95]. Downregulation of Twist not only prevented EMT but also inhibited the expression of AKR1C2, suggesting that Twist could positively regulate AKR1C2. PGPW1 is an antitumor polysaccharide. PGPW1 not only inhibited the invasion and migration phenotype of HGC-27 and EMT in a dose-dependent manner but also downregulated Twist and AKR1C2 [96]. PGP2a is an antibiotic polysaccharide extracted from ginseng too. With the increase of PGP2a concentration, its gradient decreased the protein of Twist and AKR1C2 in gastric cancer cells and caused cell apoptosis [97]. We speculated that PGPW1 and PGP2a might inhibit cancer through the Twist/AKR1C2 axis. Oxaliplatin is one of the common chemotherapy drugs for gastric cancer, which kills cancer cells by inhibiting DNA replication and transcription [98, 99]. Compared with the gastric cancer cell line TSGH, AKR1C1-AKR1C3 showed higher expression in oxaliplatin-resistant cells TSGH-S3 [45]. Inhibition of AKR1Cs with siRNA or drugs made TSGH-S3 more sensitive to oxaliplatin and cisplatin. AKR1Cs are downstream factors of Nrf2. The reduction of Nrf2 downregulated the expression of AKR1Cs and reversed the drug resistance of TSGH-S3, which indicated that regulation of the Nrf2/AKR1Cs axis had the ability to change tumor drug resistance. Zhou et al. collected information on gastric cancer patients from many databases and found that AKR1C2 was an independent factor in evaluating the prognosis of gastric cancer [100]. Patients with high expression of AKR1C2 had poor survival probability. In addition, the risk score consisting of 14 genes, including *AKR1C2*, was also valuable for evaluating the prognosis of gastric cancer patients. In general, AKR1C2 may play a role in promoting cancer in gastric cancer by promoting malignant phenotype and improving drug resistance, and the expression of AKR1C2 can be used to predict the prognosis of patients with gastric cancer.

Esophageal cancer. Esophageal cancer patients have a high mortality rate, with a 5-year survival rate of only 10–30% [101]. Among the common pathological types of esophageal cancer, most of them are squamous cell carcinoma (ESCC), 14% are adenocarcinoma (EAC) [102]. AKR1C2 was significantly overexpressed in ESCC tissues compared to paired peripheral normal tissues [103]. Patients with high AKR1C2 were more likely to have large tumor, lymph node metastases, advanced pathological stage, and more potential for vascular invasion. AKR1C2 was an independent prognostic factor of ESCC. The higher expression level of AKR1C2 predicted the shorter OS of patients. In cell and animal experiments, AKR1C2 not only promoted the proliferation, EMT, and cisplatin resistance of esophageal squamous cancer cells but also positively regulated the PI3K/Akt pathway. Targeting AKR1C2 might be a new option for ESCC treatment. It was found that AKR1C2 expression was absent in normal esophageal cells and most adenocarcinoma cell lines, but increased in metaplasia and dysplasia cell lines [104]. The tissue biopsy also showed similar results. In the lower esophageal cancer, the expression of AKR1C2 in adenocarcinoma was not only significantly lower than that in non-erosive reflux disease, erosive reflux disease, and Barrett's esophagus tissues but also lower than that in the paired squamous tissues. The study of Nancarrow et al. also confirmed the low expression of the *AKR1C2* gene in EAC [105]. We observed that the expression of AKR1C2 was inconsistent in different pathological types, suggesting that there might be heterogeneity between different pathological subtypes, which needs more research to verify later.

Liver cancer. Liver cancer has no obvious symptoms at the early stage, most of them are in the advanced stage when diagnosed, and the 5-year survival rate is less than 20% [68]. In 2020, more than 80,000 people died of liver cancer worldwide, almost equal to the number of cases. The treatment of liver cancer still faces great challenges [47].

In liver cancer cells, *AKR1C2* is the downstream factor of the *AEG1* gene, which could be positively regulated by AEG-1 [106]. *In vitro* experiments, the knockdown of either AEG-1 or AKR1C2 reduced the invasion and migration ability of hepatocellular carcinoma (HCC) cells and reversed the EMT of HCC cells. Conversely, increased expression of AEG-1 or AKR1C2 promoted the occurrence of EMT and made HCC cells more aggressive. The expression levels of AEG-1 and AKR1C2 in human liver cancer tissues were also higher than those in the paired tissues. Zhao et al. explored the expression of AKR1C2 in liver cancer through data mining [107]. According to the data from the Cancer Cell Lines Encyclopedia (CCLE), the average expression of AKR1C2 in liver cancer cell lines ranked second among all cancers. In Gene Expression Profiling Interactive Analysis (GEPIA), AKR1C2 expression in liver cancer was significantly higher than that in normal liver samples. In addition, K-M curves also suggested that high AKR1C2 levels tended to predict poor outcomes in patients. Therefore, based on the experimental data and bioinformatics results, it is not difficult to conclude that AKR1C2 plays the role of an oncogene in liver cancer and may become an important marker to assess the prognosis of liver cancer.

Urinary system cancer. Both bladder cancer and kidney cancer belong to urinary system tumors. In 2020, more than 430,000 people were diagnosed with kidney cancer, and the incidence of kidney cancer is increasing every year [47]. Clear cell renal carcinoma (CCRC) is the most common pathological type of kidney cancer. AKR1C2 was a prognostic factor of CCRC. The overall survival rate of patients with low AKR1C2 level was higher than those

with high AKR1C2 level [108]. In addition, AKR1C2 was positively regulated by DIO1. Environmental and industrial pollution may trigger bladder cancer [109–111]. In heavy industrial areas of Taiwan, the incidence of bladder cancer was significantly increased. AKR1C2 was highly expressed in the tumor tissues of these patients, which was closely related to tumor invasion. Cisplatin-containing chemotherapy is recommended for advanced bladder cancer [112], however, the emergence of cisplatin resistance may affect the treatment of bladder cancer. AKR1C2 expression was increased in cisplatin-resistant bladder cancer cells, which could induce cisplatin resistance and reduce intracellular ROS levels after cisplatin treatment [19]. Silencing or 5β cholinic targeted inhibition of AKR1C2 reversed the cisplatin resistance of cisplatin-resistant cells and made ROS production increased after cisplatin treatment.

Gynecological cancer. Cervical cancer and ovarian cancer are common gynecological malignancies, and the sum of their incidence rates is nearly 10% in females, which is a serious threat to women's health [47]. Platinum drugs are widely used in the chemotherapy of gynecological tumors [76, 113, 114]. Therefore, cisplatin insensitivity becomes a major problem in the treatment of gynecological tumors. Compared with parent cells, AKR1C2 was highly expressed in cisplatin-resistant cells of cervical cancer and ovarian cancer, which increased the resistance to chemotherapy drugs for gynecological tumors, such as cisplatin or its derivative carboplatin [115–119]. Low ROS level and high resistance to H_2O_2 and tert-butyl hydroperoxide were also observed in ovarian cells with high AKR1C2 [120]. Targeting AKR1C2 may increase the sensitivity of tumor cells to cisplatin, which is very important for the treatment of gynecological tumors. HPV infection is the most pathogenic factor of cervical cancer [121, 122]. AKR1C2 also acts as a member of the dihydrodiol dihydrogenase (DDH). High expression of DDH was detected in most HPV-positive cervical cancer patients, and DDH was closely associated with higher FIGO staging, lymph node metastasis, Ki-67, and other clinicopathological factors [123]. Perhaps due to the technology at that time, Ueda et al. did not subdivide DDH. Therefore, the relationship between AKR1C2 and cervical cancer patients still needs further research to clarify.

Nonmelanoma skin cancer. White race, long-term exposure to ultraviolet rays or chemical poisons will accelerate skin aging and increase the risk of skin cancer [124–127]. KEAP1/Nrf2/ARE is an important way to prevent oxidative stress in the body [128]. In immortalized human epidermal cells HaCaT, knockdown of KEAP1 or sulfaphane (SFN) could increase the expression of AKR1C2. When Nrf2 was downregulated, the opposite result appeared. Arsenic is a carcinogen, which can induce skin cancer in long-term contact with the skin [129, 130]. Long-term culture of HaCaT cells using arsenic-containing media stimulated the cells to enter a state of oxidative stress [131]. Keratinocytes defended against arsenic stimulation by upregulating phase II detoxifying enzymes (stage II metabolic enzymes) including AKR1C2. The activation of the antioxidant mechanism might be one of the potential mechanisms of arsenic carcinogenicity. Normal human epithelial keratinocytes (NHEKs) have a very unique growth cycle [132, 133]. After experiencing the exponential growth phase (Y) and the sense plateau phase (S), cells spontaneously get into the post-sense neutral emergency phase (E), to get rid of aging, return to the cell cycle and start to divide. Finally, cells possess tumorigenic potential. The expression of AKR1C2 gradually increased in the Y, S, E phases, the downregulation of AKR1C2 inhibited the transformation of senescent cells and growth activity [134].

Other cancers. In addition to the aforementioned cancer types, AKR1C2 is also associated with other tumors. On the basis of human glioma cell lines U373 and T98G, a 4-fold increase in AKR1C2 was observed through the long-term treatment with temozolomide (TMZ) [135]. High levels of AKR1C2 were also detected in cisplatin-resistant oral cancer cells, and the sensitivity of cisplatin and 5-fluorouracil (5-FU), an antitumor drug that inhibits DNA synthesis by interfering with the nucleotide synthetic enzyme thymidylate synthase, increased after the silencing of AKR1C2 [116, 136]. AKR1C2, a ferroptosis-related gene, was differentially expressed in acute myeloid leukemia (AML) patients and healthy people, which was an independent prognostic factor in AML patients [137]. The expression of AKR1C2 was significantly lower in AML patients, however, the high expression of AKR1C2 signified a poor prognosis.

AKR1C2 inhibitors

AKR1C2 can enhance treatment resistance in multiple cancer types (Table 1), hence we speculate that AKR1C2 may be a potential target for tumor therapy. We summarized the reagents presented above that can inhibit the

Table 1. AKR1C2 induces therapy-resistance in tumors.

	Types of Cancer	Treatment	References
AKR1C2	Bladder Cancer	Cisplatin	[19]
	Cervical Cancer	5-FU	[116]
		Cisplatin	[115, 116]
	Esophageal Cancer	Cisplatin	[103]
	Lung Cancer	Adriamycin	[84]
		Carboplatin	[115]
		Cisplatin	[84, 86, 87, 115]
		Radiation	[84]
	Oral Cancer	5-FU	[116]
		Cisplatin	[116]
	Ovarian Cancer	Carboplatin	[115]
		Cisplatin	[115, 120]
	Prostate Cancer	Adriamycin	[62]
		Cisplatin	[62]
AKR1Cs	Gastric Cancer	Cisplatin	[45]
		Oxaliplatin	[45]

Table 2. Function of AKR1C2 inhibitors in tumors.

Reagents	Target	Types of cancer	Inhibiting the function	References
5β-cholanic acid	AKR1C2	Bladder Cancer	Cisplatin resistance	[19]
Flufenamic acid	AKR1Cs	Gastric Cancer	Oxaliplatin resistance	[45]
Indomethacin	AKR1Cs	Prostate Cancer	Decompose ^{3}H-DHT	[21]
MCA	AKR1Cs	Gastric Cancer	Oxaliplatin resistance	[45]
Mefenamic acid	AKR1Cs	Cervical Cancer	Cisplatin resistance and 5-FU resistance	[116]
	AKR1Cs	Oral Cancer	Cisplatin resistance and 5-FU resistance	[116]
Phenolphthalein	AKR1Cs	Gastric Cancer	Oxaliplatin resistance	[45]
Sex hormones	NNK reductases (including AKR1C2)	Lung Cancer	Metabolize NNK to NNAL	[92]
Tolmetin	AKR1Cs	Prostate Cancer	Decompose ^{3}H-DHT	[21]
UDCA	AKR1C2	ESCC	Proliferation, migration, and EMT	[103]
	AKR1C2	Prostate Cancer	Convert 5α-DHT to 3α-diol	[53]

function of AKR1C2 (Table 2). Chemotherapy resistance of tumor cells induced by AKR1C2 could be reversed by α-methylcinnamic acid, 5β-cholanic acid, flufenamic acid and mefenamic acid, phenolphthalein [19, 45, 116]. As a selective inhibitor of AKR1C2, ursodeoxic acid (UDCA) could inhibit the proliferation, migration, and EMT of ESCC induced by AKR1C2 [103]. In prostate cancer, the ability of AKR1C2 to decompose DHT was inhibited by indomethacin, tolmetin, and UDCA [21, 53]. With the exception of the drugs mentioned above, some compounds could also inhibit the vitality of AKR1C2, such as bill acid methyl esters and organizational compounds [138, 139]. Six of the 11 kinds of bill acid methyl esters inhibited more than half of AKR1C2 activity [138]. Apart from the inhibition of AKR1C2, organizational compounds could play an anti-cancer role in inhibiting the proliferation and migration of ovarian cancer cells [139].

In conclusion, reviewing the literature, we found that AKR1C2 plays an important role in tumor and steroid hormone metabolism. Therefore, we must explore the effects of AKR1C2 on the tumor from both hormone-dependent and hormone-independent aspects.

In hormone-dependent tumors, AKR1C2 mainly plays an anti-tumor role in prostate cancer and breast cancer, because AKR1C2 can metabolize carcinogenic DHT and P4 into weaker hormones. Due to the metabolic effect of AKR1C2 on P4, there is no P4 antagonistic to estrogen. AKR1C2 may play an oncogenic role in endometrial cancer with a large probability.

In hormone-independent tumors, except for esophageal adenocarcinoma, AKR1C2 can promote the occurrence and development of most tumors. High AKR1C2 will take poor prognosis for patients. AKR1C2 can be used as a prognostic indicator for patients with gastric cancer, liver cancer, CCRC, and other tumors. In addition, the high expression of AKR1C2 in drug-resistance tumor cells was observed, which was closely related to the activation of the Keap1-Nrf2-ARE pathway, suggesting that AKR1C2 is an important member of the tumor drug resistance mechanism. Targeting AKR1C2 may become an effective tumor therapy.

Here, we have synthesized the related drugs that inhibit AKR1C2 in different tumors. However, the inhibition of these reagents on AKR1C2 has only been confirmed *in vitro*. We believe that with further research, more inhibitors will be developed and used in *in vivo* research in the future.

At present, AKR1C2 has not been studied extensively. This review summarizes the existing literature and attempts to clarify the role of AKR1C2 in malignant tumors. Because of the technical, experimental conditions or other reasons, most researchers only stayed at the surface of the study on the impact of AKR1C2 on tumors instead of conducting in-depth research on the mechanism of AKR1C2. Which downstream factors or signal pathways will be regulated by AKR1C2 is worthy of further discussion and research. Therefore, the research on AKR1C2 can't be stopped.

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