AKR1B10 in Physiology and Pathophysiology

Subjects: Cell Biology

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AKR1B10 is a human nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reductase belonging to the aldo-keto reductase (AKR) 1B subfamily. It catalyzes the reduction of aldehydes, some ketones and quinones, and interacts with acetyl-CoA carboxylase and heat shock protein 90α. The enzyme is highly expressed in epithelial cells of the stomach and intestine, but down-regulated in gastrointestinal cancers and inflammatory bowel diseases. In contrast, AKR1B10 expression is low in other tissues, where the enzyme is upregulated in cancers, as well as in non-alcoholic fatty liver disease and several skin diseases. In addition, the enzyme's expression is elevated in cancer cells resistant to clinical anti-cancer drugs. Thus, growing evidence supports AKR1B10 as a potential target for diagnosing and treating these diseases. Herein, we reviewed the literature on the roles of AKR1B10 in a healthy gastrointestinal tract, the development and progression of cancers and acquired chemoresistance, in addition to its gene regulation, functions, and inhibitors.

Keywords: aldo-keto reductases ; AKR1B10 ; biomarkers

1. Introduction

Aldo-keto reductases (AKRs) are a group of NAD(P)(H)-dependent enzymes catalyzing interconversions between the carbonyl and alcohol groups of endogenous and xenobiotic compounds [1]. The AKR superfamily is systematized into 16 families: AKR1 (aldehyde reductases, aldose reductases, hydroxysteroid dehydrogenases, and steroid 5b-reductases); AKR2 (mannose and xylose reductases); AKR3 (yeast AKRs); AKR4 (chalcone and codeinone reductases); AKR5 (gluconic acid reductases); AKR6 (β-subunits of the potassiumgated voltage channels); AKR7 (aflatoxin dialdehyde and succinic semialdehyde reductases); AKR8 (pyridoxal reductases); AKR9 (aryl alcohol dehydrogenases); AKR10 (*Streptomyces* AKRs); AKR11 (*Bacillus* AKRs); AKR12 (*Streptomyces* sugar aldehyde reductases); AKR13 (hyperthermophilic bacteria reductases); AKR14 (*Escherichia coli* reductases), AKR15 (*Mycobacterium* reductases), and AKR16 (*Vibrio cholerae* reductases). Each family is further divided into several subfamilies based on a >60% amino acid sequence identity. To date, fifteen AKR members have been identified in humans and belong to the AKR1A, AKR1B, AKR1C, AKR1E, AKR6A, and AKR7A subfamilies. There are three members of the human AKR1B subfamily: AKR1B1 (aldose reductase), AKR1B10 (aldose reductase-like protein-1), and AKR1B15, whose genes are clustered at chromosome 7q33 [1]. AKR1B1, AKR1B10, and an enzymatically active isoform of AKR1B15 are 36-kDa soluble monomeric proteins consisting of 316 amino acids and sharing >68% amino acid sequence identity, of which 91.5% are shared between AKR1B10 and AKR1B15 [2][3]. The three AKRs are NADPH-dependent reductases and display overlapping substrate specificities for aromatic and aliphatic aldehydes but differ in their catalytic efficiencies [2][3][4][5][6], which is notably higher for retinal (all-*trans*-retinaldehyde) in AKR1B10 [5]. In addition, the glucose reductase activity characteristics of AKR1B1 are very low for AKR1B10 and AKR1B15 [2][4][5], and prostaglandin F synthase activity is observed with AKR1B1, but not with AKR1B10 [7]. In contrast to AKR1B1, AKR1B10 and AKR1B15 exhibit low 17β-hydroxysteroid dehydrogenase activity for estrone and 4-androstene-3,17-dione [3][6]. For subcellular localization, AKR1B1 and AKR1B10 are cytosolic, whereas AKR1B15 is in the mitochondria [3]. The three AKR1Bs also have different tissue distributions. While AKR1B1 is ubiquitous, AKR1B10 protein is predominantly expressed in the human stomach and intestine [2][8], although its mRNA is detected in many other tissues [3][8][9]. The mRNA for AKR1B15 is predominantly expressed in the placenta, testis, skeletal muscle, and adipose tissue, where its level is lower than that of mRNA for AKR1B10 [3].

While the most studied enzyme of the AKR1B subfamily is AKR1B1, which has been implicated in the pathogenesis of diabetes complications and inflammatory disease [10][11], many studies of AKR1B10 have focused on its association with cancers and other diseases since its overexpression in hepatocellular carcinomas (HCC) was found in 1998 [12]. In addition to its role in gastrointestinal homeostasis, increasing evidence suggests that the aberrant expression of AKR1B10 promotes its diagnostic and prognostic utility as a potential tumor biomarker and elucidates its role in carcinogenesis, tumor progression, and the development of chemoresistance. In this review, we summarize recent progress towards

understanding the gene regulation of AKR1B10 and its functions in gastrointestinal physiology, the pathogenesis of several cancers and skin diseases, and acquired drug resistance. Based on the available evidence, we propose that AKR1B10 is thus a potential target for drug discovery. We also provide a brief overview of AKR1B10 inhibitors.

2. Gene Regulation of AKR1B10

2.1. Factors Regulating AKR1B10 Expression

AKR1B10 is induced in various types of cancer tissues and down-regulated in gastrointestinal cancers. In addition to tumor progression, changes in AKR1B10 expression levels are associated with several noncanceraous diseases and chemoresistance (as described later). Thus, AKR1B10 expression is an important factor in the pathogenesis of these diseases. However, the molecular mechanisms of AKR1B10 gene regulation have not been fully elucidated.

Nucleotide sequence analysis of the 5′-flanking region of AKR1B10 gene revealed the existence of putative TATA box, CAAT box, p53, AP-1, and antioxidant response elements (ARE) [13][14]. There is a complex microsatellite composed of repetitive C and T sequences, which are highly polymorphic and may affect the expression of AKR1B10 (Figure 1). We found polymorphism at this microsatellite in the human lung adenocarcinoma A549 cell line, but no significant difference in promoter activity was observed in the gene reporter assay analysis [14].

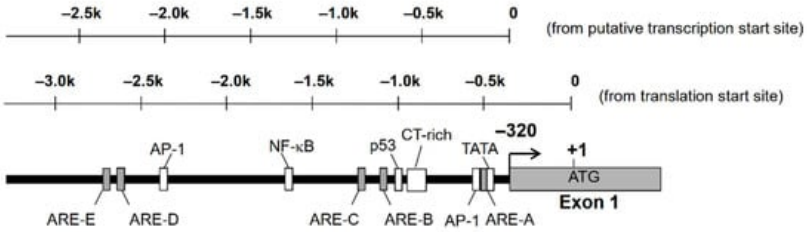

Figure 1. Putative transcription factor binding sites on the 5′-flanking region of AKR1B10 gene.

AKR1B10 expression is affected by treatment of human cultured cells with various agents (Table 1). Most of the agents upregulate AKR1B10, whereas a phorbol ester 12-*O*-tetradecanoylphorbol 13-acetate (TPA) down-regulates the expression [15]. 5-Fluorouracil (5-FU) and oxaliplatin (L-OHP) exhibit opposite effects on the AKR1B10 expression depending on colorectal cancer (CRC) cell lines [16]. Regulators and signal molecules involved in the modulation of AKR1B10 expression by several agents are also listed in Table 1.

Table 1. Agents that modulate AKR1B10 expression.

Agent *	Signal Molecule	Cell **	References
Up-regulation			
Ethoxyquin	**Nrf2**	**Lung cancer A549, H23**	[14]
MG-132, bortezomib	**Nrf2**	**CRC SW-480, HT29**	[17]
Doxorubicin	**Nrf2**	**Gastric cancer MKN45**	[18]
EGF, insulin	**AP-1, ERK**	**HCC HepG2, Hep3B**	[19]
Lipopolysaccharide		**Blood mononuclear cells**	[20]
BMP, IBMX		**Mesenchymal stem cells**	[21]
9,10-Phenanthrenequinone	**Nrf2, ERK**	**Lung cancer A549**	[22]
Cigarette smoke extract		**Airway epithelium**	[23]
Carnosic acid, *t*-BHQ	**Nrf2**	**Astrocytoma U373MG**	[15]
5-FU, L-OHP	**p53**	**CRC HT116**	[16]
Down-regulation			
TPA	**c-Jun, ERK**	**Lung cancer A549**	[15]
5-FU, L-OHP		**CRC HT29**	[16]

Note: * Abbreviations of agents: EGF; epidermal growth factor, BMP, bone morphogenetic protein 2; IBMX, 3-isobutyl-1-methylxanthine; *t*-BHQ, *t*-butyl hydroquinone; 5-FU, 5-fluorouracil; L-OHP, oxaliplatin; TPA, 12-*O*-tetradecanoylphorbol 13-acetate. ** Abbreviations of cancer: CRC, colorectal cancer; HCC, hepatocellular cancer.

2.2. Contribution of Nrf2 to AKR1B10 Induction

An antioxidant (ethoxyquin) induces AKR1B10 expression in lung cancer cell lines A549 and H23 [14]. Ethoxyquin is known to activate the transcription factor Nrf2 (NF-E2-related factor). Furthermore, increased AKR1B10 promoter activity caused by ethoxyquin was suppressed by the introduction of dominant-negative Nrf2 protein in the gene reporter assay. In addition, the introduction of Nrf2 augmented promoter activity, indicating that AKR1B10 gene transcription is regulated by Nrf2. Nrf2 is a member of the Cap'n'Collar family of basic leucine zipper transcription factors known to be activated by various antioxidants or reactive oxygen species (ROS). Nrf2 forms a heterodimer with small Maf proteins and binds to the ARE of target genes [24][25]. In non-stimulated cells, Nrf2 is trapped, leading to ubiquitin-dependent degradation by Kelch-like ECH-associated protein 1 (Keap1). Once the cells are stimulated, the Keap1 protein is oxidatively modified and releases Nrf2, allowing its nuclear localization [26][27]. It has been suggested that Nrf2 is involved in the up-regulation of AKR1B10 by proteasome inhibitors [17], 9,10-phenanthrenequinone [22], and doxorubicin [18]. In addition, microarray analyses consistently indicate that the Keap1/Nrf2 pathway is involved in AKR1B10 gene regulation [28][29][30]. We demonstrated in the gene reporter assay that the introduction of dominant-negative Nrf2 protein also leads to a reduction in basal transcriptional activity of AKR1B10 in A549 cells, where AKR1B10 is highly expressed. However, the treatment failed to show any effect in H23 cells where AKR1B10 expression was very low, suggesting that Nrf2 participates in the basal expression of AKR1B10 [31]. Thus, the Keap1/Nrf2 pathway is one of the major regulatory systems for AKR1B10 gene regulation.

The Nrf2 ARE consensus sequence is 5′-TGACnnnGC-3′, and there are at least five potential AREs found in the 5′-flanking region, up to −3282 bp from the translation start site (−2962 bp from the putative transcription start site). We indicated that only AREs located between −530 bp and −522 bp (between −210 bp and −202 bp from the transcription start site, ARE-A) are functional among these five AREs [31]. There is an AP-1 site (between −540 bp and −532 bp) just upstream of this ARE. The consensus sequence of AP-1 is 5′-TGACTCA-3′, and the corresponding nucleotide sequence of the AKR1B10 gene, 5′-TGACTCATC-3′, resembles the ARE. In fact, the introduction of a mutation in the AP-1 site resulted in a reduced response to Nrf2 in the gene reporter assay. Accordingly, this AP-1 site may function as an ARE, and this tandem repeat of AREs may be important for a strong response to stimulations targeting Nrf2 [31] (Figure 2).

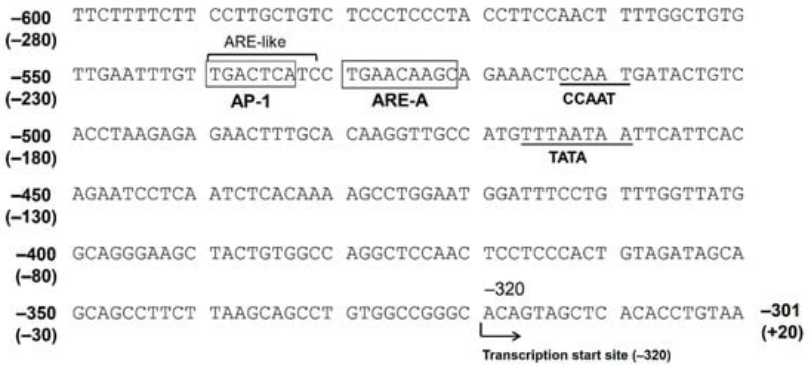

Figure 2. The nucleotide sequence of the 5′-flanking region of the AKR1B10 gene. The numbers represent the nucleotide position when +1 is defined as the translation start site. The numbers in parentheses represent the position when +1 is defined as the putative transcription start site.

2.3. The Function of AP-1 Protein in AKR1B10 Gene Regulation

The induction of AKR1B10 by EGF and insulin in HepG2 cells also shows the importance of the AP-1 site [19]. The AP-1 protein consists of a heterodimer of c-Jun and c-Fos proteins binding to the AP-1 site [32]. Cell treatment with EGF or insulin significantly increases the amount of AP-1 protein. The introduction of c-Jun and c-Fos proteins also augments transcriptional activity in gene reporter assays. Interestingly, the injection of c-Fos shRNA to HepG2-inoculated mice to knockdown c-Fos results in the loss of AKR1B10 expression, suggesting that endogenously expressing c-Fos is an important regulator in the expression of AKR1B10. Furthermore, Cheng et al. [33] have proposed that AP-1 is involved in the induction of AKR1B10 in HCC cells. They show that the knockdown of interleukin-1 associated kinase 1 (IRAK1) leads to a decrease in AKR1B10 expression possibly mediated through regulating AP-1 signal transduction.

On the other hand, the c-Jun component of AP-1 protein has the opposite function on AKR1B10 gene regulation. We have shown that TPA downregulates AKR1B10 expression through the induction of c-Jun protein in A549 cells [15]. In addition,

the forced expression of c-Jun protein in A549 cells resulted in decreased AKR1B10 expression, and the introduction of c-Jun in gene reporter assays led to the suppression of transcriptional activity in an AP-1 site-independent manner. The leucine zipper domain is necessary for c-Jun to exhibit its suppressive action, indicating that c-Jun needs to interact with other proteins. Hence, c-Jun also acts as a negative regulator. Although it is not clear how c-Jun acts differently, the variations of other protein factors existing in the cells, such as c-Fos protein, may determine the action of c-Jun.

2.4. Signal Transduction

The cAMP-dependent signaling pathway may take part in the regulation of AKR1B10, because a phosphodiesterase inhibitor, IBMX, with BMP2, is able to induce AKR1B10 expression [21]. Since a potential cAMP-response element (CRE) has not been identified in the AKR1B10 gene promoter region to date, it could be that this pathway might modify the other signaling cascades. Extracellular signal-regulated kinase (ERK), a mitogen-activated protein kinase (MAPK), is an important signal molecule in AKR1B10 gene regulation. The induction of AKR1B10 by EGF and insulin is mediated through the activation of ERK in HepG2 cells, and totally abolished by the inhibition of its upstream kinase, MAPK/ERK kinase (MEK) [19]. Thus, the receptor tyrosine kinase/ERK cascade is one of the primary signaling pathways involved in the induction of AKR1B10. In addition, ERK regulates the basal expression of AKR1B10 in this cell line as well as in A549 cells, which is suggested by studies using MEK inhibition [15]. On the other hand, ERK activation is also a key event in the TPA-mediated down-regulation of AKR1B10. The inhibition of MEK resulted in decreased c-Jun induction, leading to the loss of TPA's action. It is very interesting that ERK activation is involved in both up-regulation and down-regulation of AKR1B10 expression as seen in the case of c-Jun.

Recently, p53 protein, a tumor suppressor gene product, was shown to play a key role in determining whether AKR1B10 expression is upregulated or down-regulated. In CRC HT29 cells possessing mutant p53, treatment with 5-FU or L-OHP reduced AKR1B10 expression. Alternatively, expression was induced by these agents in c CRC HCT116 cells having wild-type p53. When the p53 gene in HCT116 cells is knocked-down, 5-FU can no longer induce AKR1B10 [16]. Thus, p53 protein might act as a switch to determine the direction of AKR1B10 expression, suggesting that the level and status of p53 might be an important factor.

The gene regulation pathways for AKR1B10 are summarized in Figure 3. As described above, we still have little knowledge of the mechanisms underlying AKR1B10 gene regulation. The regulation pathways appear to be complex, since, for example, the same factors can produce opposing outcomes. There are likely more factors involved, and therefore, further investigations are necessary to solve the puzzle of gene regulation of AKR1B10 and its physiological significance.

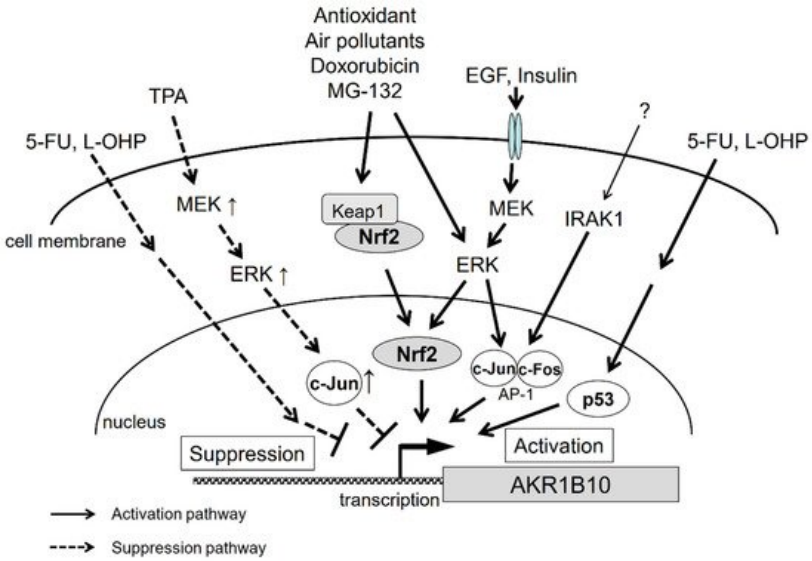

Figure 3. Signal transduction pathways that regulate AKR1B10 gene expression.

3. Conclusions

Functional studies reveal that AKR1B10 physiologically contributes to the maintenance of cellular homeostasis through the detoxification of cytotoxic RCS and regulating the metabolism of isoprenoid, retinoid, and lipid. AKR1B10 expression is constitutively high in the epithelial cells of the gastrointestinal tract, where the enzyme plays a critical role in epithelial cell renewal and the metabolism of several therapeutic drugs and carbonyl compounds produced by gut bacteria.

Clinical and basic research has proven that AKR1B10 is down-regulated in gastrointestinal cancers and several inflammatory bowel diseases, proposing that its low expression is correlated with poor prognosis and decreased survival for patients with CRC and gastric cancer. By contrast, in other tissues with normally low or no expression, the evidence is mounting that AKR1B10 is upregulated and involved in several forms of cancer and inflammatory disease. In addition, AKR1B10 is increased and implicated in the acquisition of anti-cancer drug resistance. In liver, lung, and breast cancers, AKR1B10 may be upregulated through the activation of stress-induced signal transduction pathways (such as Nrf2, AP-1, and MAPK pathways) and related to the proliferation and migration of cancer cells. However, the mechanisms underlying AKR1B10 down-regulation and its association with gastrointestinal diseases have been poorly elucidated. Thus, AKR1B10 acts as a double-edged sword depending on the type of cancer cells, and further understanding its role in the onset and progression of these diseases should be pursued.

A number of AKR1B10 inhibitors have been developed, of which HCCFA, the most potent, significantly inhibits not only the migration, proliferation, and metastasis of lung cancer A549 cells, but also the metastatic and invasive abilities of cisplatin-resistant A549 cells. Therefore, utilizing AKR1B10 inhibitors for cancers that highly express AKR1B10 is expected in clinical practice. Since no genes encoding homologues of human AKR1B10 were identified in experimental animals such as rats and mice [34][35], the efficacy and pharmacokinetics of the AKR1B10 inhibitors in vivo are unclear, and as such, further studies are needed to develop a more clinically relevant approach.

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