Regulation of aldo–keto reductases in human diseases

Wei-Dong Chen and Yanqiao Zhang *

Department of Integrative Medical Sciences, Northeast Ohio Medical University, Rootstown, OH, USA

INTRODUCTION

The aldo–keto reductases (AKRs) are a superfamily of NAD(P)H-linked oxidoreductases, which primarily catalyze the reduction of aldehydes and ketones to primary and secondary alcohols, respectively (Penning and Drury, 2007). AKRs are generally soluble, cytosolic monomeric (37 kDa) enzymes and are present in both prokaryotes and eukaryotes. These enzymes share a common protein fold, a (β/α)8 or a triosephosphate isomerase (TIM)-barrel, and have an active site in the C-terminal face (Ice et al., 1997a,b; Barski et al., 2008). Most AKRs use pyridine nucleotide as cofactors and catalyze simple oxidation–reduction reactions involved in the metabolism of sugar aldehydes, reactive lipid aldehydes, ketoprostaglandins, and ketosteroids.

Aldo–keto reductases consist of 15 families which have more than 100 members (Barski et al., 2008). There are 13 human AKR proteins that fall into 3 families AKR1, AKR6, and AKR7 (Table 1). The detailed information is available at http://www.med.upenn.edu/akr, an AKR superfamily homepage, maintained by Dr. T. Penning at the University of Pennsylvania. The human AKR enzymes include AKR1A1 (aldehyde reductase), AKR1B1 and AKR1B10 (aldose reductases), AKR1C1–C4 (hydroxysteroid dehydrogenases), AKR1D1 (steroid 5β-reductase), the AKR6 family (AKR6A3, A5, and A9; Kβ proteins), and the AKR7 family (AKR7A2 and AKR7A3; aflatoxin aldehyde reductases). These human AKR enzymes can catalyze many metabolic oxidation–reduction reactions of numerous endogenous and exogenous substrates, including glucose, steroids, carcinogens, reactive aldehydes, and a variety of carbonyl-containing drugs. To date, the AKR enzymes have been implicated in a number of human diseases. It is known that AKR1A1, AKR1B10, and AKR1C1–C3 are involved in tobacco-induced carcinogenesis (Hsu et al., 2001; Penning, 2005; Jin and Penning, 2007; Zhang et al., 2008; Liu et al., 2009a). Inhibition of AKR1B1 is able to alleviate diabetic complications. Through mediating oxidative-stress-induced inflammatory signals, AKR1B1 plays a role in inflammation-related diseases such as sepsis and colon cancer (Ramana, 2011). AKR1B1 and AKR1B10 regulate the development and progression of human liver, breast, and lung cancers through detoxifying reactive carbonyls, retinoic acid homeostatic regulation, and lipid metabolism (Liu et al., 2009a; Diez-Dacal et al., 2011). AKR1C1–C3 enzymes are involved in prostate and breast carcinogenesis (Penning and Byrns, 2009). Mutations in AKR1D1 gene in patients lead to neonatal cholestasis, hepatitis, and liver failure (Lemonde et al., 2003; Barski et al., 2008). AKR7A proteins protect liver from acetaminophen-induced hepatotoxicity by enhancing hepatocellular antioxidant defense (Ahmed et al., 2011). Because AKR enzymes are increasingly being recognized to play a role in various diseases, understanding the regulation of human AKR genes may help us develop novel therapeutic approaches. In this review, we summarize the regulation of AKRs by transcription factors, mediators, and pathological conditions.

THE REGULATION OF AKRs

Many transcription factors have been identified to regulate the expression of human AKR genes, which could have profound effects on the metabolism of endogenous mediators and detoxication of chemical carcinogens. Several classes of transcription enhancer elements have been identified in the upstream promoter region of AKR genes that include nuclear receptor response elements, AP-1 binding sites, the xenobiotic response elements (XRE), osmotic response elements (ORE), estrogen response elements (ERE), and antioxidant response elements (ARE; Ko et al., 1997; Burczynski et al., 1999; Lou et al., 2006; Penning and Drury, 2007).

AKR1A1

AKR1A1, a ubiquitously expressed enzyme, is a well-known cytosolic, NADPH-dependent and monomeric oxidoreductase. AKR1A1 participates in carbonyl reductions of chemotherapeutic drugs. Protein and mRNA levels of AKR1A1 in irinotecan-resistant LoVo cells are higher than in human colon adenocarcinoma LoVo cells (Peng et al., 2010). Recent studies suggest that overexpression
Table 1 | Regulation of human aldo–keto reductase.

| Name    | Enzyme                          | Previous symbols | Synonyms               | Regulation                      |
|---------|---------------------------------|------------------|------------------------|---------------------------------|
| AKR1A1  | Aldehyde reductase              | ALDR1            | hStaf/ZNF143, C/EBP    | PPARγ, atorvastatin             |
| AKR1B1  | Aldose reductase                | ALDR1            | AR                     | Thyroid hormone, CREB, NAFT5, Nrf2, nitric oxide, EGF, TGFβ1, atorvastatin |
| AKR1B10 | Aldose reductase                | AKR1B11          | AKR1B12, ALR-1, HIS, ARL1, HSI, ALDR1n | Mouse Akr1b7 is regulated by LXR, PXR, CAR, FXR |
| AKR1C1  | Dihydriodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase | DDH1             | DDH, MBAB, DD1, HAKRC  |                                   |
| AKR1C2  | Dihydriodiol dehydrogenase 2; bile acid binding protein; 3-alpha hydroxysteroid dehydrogenase, type III | DDH2             | DD, BABP, DD2, HAKRD, MCDR2 | IL-1β                            |
| AKR1C3  | Aldo–keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II) | HSD17B5          | KIAA0119, DDX, HAKRB   | IL-6, cadmium, Nrf2               |
| AKR1C4  | Chlordecone reductase; 3-alpha hydroxysteroid dehydrogenase, type I; dihydriodiol dehydrogenase 4 | CHDR             | DD4, HAKRA, C11, 3-alpha-HSD, CDR, MGC228B1 | LXR                              |
| AKR1D1  | Delta 4-3-ketosteroid-5-beta-reductase | SRD5B1          | KCNAB1, KCNA1B, hKvBeta3, Kvb1.3, hKvb3 | Estrogen                        |
| AKR6A3  | Shaker channel β-subunit (Kvb1) |                   | KCNAB2, KCNA2B, HKvbeta2.1, HKvbeta2.2 | Bone morphogen protein-2        |
| AKR6A5  | Shaker channel β-subunit (Kvb2) |                   | KCNA3B, KCNA3B         |                                  |
| AKR6A9  | Shaker channel β-subunit (Kvb1) |                   |                       |                                  |
| AKR7A2  | Aflatoxin aldehyde reductase    | AFAR             | Nrf2, acetonaminphen   |                                  |
| AKR7A3  | Aflatoxin aldehyde reductase    |                  | Nrf2, acetonaminphen   |                                  |

References and the regulation of AKRs by pathological conditions can be found in the text.

of AKR1A1 may protect lung epithelial cells against acute toxic effects of polycyclic aromatic hydrocarbon metabolites (Abedin et al., 2012).

Gel-shift assays and chromatin immunoprecipitation assays revealed that AKR1A1 is a target gene of transcription factors hStaf/ZNF143 and C/EBP homologous protein (Table 1; Barski et al., 2004; Myslinski et al., 2006). The β-hydroxy-β-methylglutaral coenzyme A (HMG-CoA) reductase inhibitor atorvastatin suppresses the expression of AKR1A1 and AKR1B1 in human umbilical vein endothelial cells (HUVEC) but not in human proximal tubular epithelial cells (Ruf et al., 2009). Luciferase reporter assays showed that atorvastatin regulates AKR1A1 promoter activity through an ARE (Ruf et al., 2009). Grip et al. (2002) show that atorvastatin also activates PPARγ. The PPARγ binding sites are also found in the AKR1A1 promoter. Thus, atorvastatin may regulate AKR1A1 expression via direct or indirect regulation of AKR1A1 promoter activity.

AKR1B1 AND AKR1B10

AKR1B1, the most studied AKR family member, is the rate-limiting enzyme of the polyol pathway. AKR1B1 has long been known for its potential role in the development of diabetic complications by driving glucose flux through the polyol pathway (Liu et al., 2009a). Because this enzyme catalyzes the reduction of glucose to a sugar alcohol, many AKR1B1 inhibitors have been developed for the treatment of diabetic complications. Recent reports showed that AKR1B1 is also involved in inflammatory diseases such as atherosclerosis, sepsis, uveitis, and colon carcinogenesis through regulating oxidative stress-induced inflammatory signals (Ramana, 2011; Shoeb et al., 2011). The AKR1B1 and AKR1B10 have 71% identify in amino acid sequence. These two proteins show overlapped substrate specificity but significantly different tissue expression patterns. AKR1B1 is ubiquitously expressed whereas AKR1B10 is mainly expressed in liver, colon, small intestine, thymus, and adrenal gland. AKR1B10 was identified in 1998. Recent results suggest that AKR1B10 may be a tumor marker of several types of cancers. For example, Wang et al. (2010) reported that smoking can induce up-regulation of AKR1B10 in the airway epithelium, suggesting that increased AKR1B10 expression may be involved in lung carcinogenesis. Increased expression of AKR1B1 and AKR1B10 has been found in human liver, breast, and lung tumors. Thus these two proteins may play a key role in the development and progression of these types of cancers (Liu et al., 2009a; Kropotova et al., 2010).

The AKR1B1 gene is up-regulated in response to thyroid hormone (T3) treatment. Liao et al. (2009) reported that T3-bound thyroid hormone receptor (TR) induced AKR1B1 expression through a T3 response element; they also demonstrated that AKR1B1 overexpression in some types of hepatocellular carcinomas (HCCs) was TR-dependent, suggesting that the TR-AKR1B1
pathway might play a crucial role in the development of HCC. LeFrancois-Martinez et al. (2004) indicated that AKR1B1 expression in human adrenocortical cells may be regulated by the transcription factor cAMP-responsive element-binding protein (CREB). Yang et al. (2006) showed that the expression of AKR1B1 is tightly regulated by the transcription factor nuclear factor of activated T-cells 5 (NFAT5) through binding to OREs in the gene. Recently, the transcription factor nuclear receptor-erythroid 2 related factor 2 (Nrf2), a key regulator in the adaptive response to oxidative stress, was shown to regulate the expression of AKR1B1, AKR1B10, and AKR1C1–C3 (Ebert et al., 2011; Nishinaka et al., 2011). Finally, several groups observed that the AKR1B1 expression is up-regulated in response to the treatment of nitric oxide (Seo et al., 2000), hydrogen peroxide, methylglyoxal (Yabedateishimura et al., 2003), epidermal growth factor, or transforming growth factor-β (Jiang et al., 2008).

The closest murine ortholog of human AKR1B10 is Akr1b7, which is also expressed in the liver, intestine, and adrenal gland. Murine Akr1b7 shares 89% amino acid homology with human AKR1B10. There are several nuclear receptor binding sites in the Akr1b7 promoter (Figure 1). Several groups have identified Akr1b7 as a direct target of nuclear receptors, such as liver X receptor (LXR; Volle et al., 2004), xenobiotic receptors pregnane X receptor (PXR), constitutive androstane receptor (CAR), and farnesoid X receptor (FXR; Figure 1). The finding that Akr1b7 is highly inducible by PXR and CAR (Liu et al., 2009b), is consistent with the role of Akr1b7 in xenobiotic metabolism and lipid peroxidation. Schmidt et al. (2011) showed that FXR induces Akr1b7 expression in the liver and intestine and that Akr1b7 plays a role in detoxification of specific bile acids. We found that hepatic and intestinal Akr1b7 is highly inducible by FXR and that Akr1b7 has striking effects on lowering blood glucose levels and reducing hepatic lipid accumulation in diabetic mice (Ge et al., 2011). These effects are associated with reduced expression of hepatic gluconeogenic genes and increased very low-density lipoprotein secretion. Our data suggest that Akr1b7 may be a therapeutic target for treatment of diabetes mellitus. It will be intriguing to investigate whether human AKR1B10 also regulates glucose and lipid metabolism.

AKR1C1–C4

AKR1C1–C4 share over 86% homology with each other. AKR1C1 is expressed in liver, kidney, and testis. AKR1C2 is mainly expressed in liver, prostate, and mammary gland. AKR1C3 is expressed in liver, brain, kidney, placenta, and testis. AKR1C4 is specifically expressed in liver. These enzymes are involved in the metabolism of steroid hormones (AKR1C1–AKR1C3), prostaglandins (AKR1C3), and bile acids (AKR1C4), and play important roles in the detoxification of drugs and xenobiotics (Ebert et al., 2011). AKR1C1–C3 enzymes may be involved in tobacco-induced prostate and breast carcinogenesis (Penning and Byrns, 2009). Increased expression of AKR1C1 has been detected in human diseases, such as endometriosis (Smuc et al., 2009; Hevir et al., 2011), androgen-independent prostate cancer (Stanbrough et al., 2006), and lung cancer (Hsu et al., 2001). Increased expression of AKR1C3 is found in leukemia (Mahadevan et al., 2006; Birtwistle et al., 2009), prostate cancer (Fung et al., 2006; Stanbrough et al., 2006), and breast cancer (Penning and Byrns, 2009).

AKR1C1 overexpression has been associated with drug-resistance in a variety of cancers (Deng et al., 2002, 2004; Chen et al., 2005; Hung et al., 2006). Some anticancer drugs may be metabolized by AKR1C1 due to the high similarity between the chemical structures of these drugs and AKR1C1 substrates (Selga et al., 2008). It has been proposed that increased AKR1C1 activity would detoxify reactive oxygen species induced by drugs such as cisplatin, and could lead to apoptosis-related development of drug-resistance. Selga et al. (2008) suggest that AKR1C1 gene expression is regulated by Sp1 transcription factor, and suppression of AKR1C1 by RNA interference (RNAi) improves the sensitivity to methotrexate, an antimitabolite drug for the chemotherapy of human malignancies, in methotrexate sensitive HT29 cells. The transcription factor, nuclear factor-Y (NF-Y) has also been reported to directly regulate the basal transcription of AKR1C1 in human ovarian, lung, and liver carcinoma cells (Pal-lai et al., 2010). Interleukin 1β (IL-1β), a major proinflammatory cytokine, can significantly induce the expression of both AKR1C1 and AKR1C2. Roberson et al. (2011) recently showed that this cytokine can facilitate local progesterone metabolism in a cell type critical for maintaining cervical structure through regulating
expression of AKR1C1 and AKR1C2. Chun et al. (2009) reported that IL-6 induces the expression of AKR1C3. Cadmium is a toxic metal. Occupational exposure to cadmium is related to the development of lung cancer. Lee et al. (2011) reported that cadmium induces AKR1C3 gene expression through activation of PI3K-related intracellular signaling pathways and Nrf2 activation. The significance in induction of AKR1C3 by IL-6 or cadmium remains to be explored.

It is well documented that liver X receptor (LXR), a nuclear receptor for oxysterols, plays an important role in the regulation of bile acid, lipid, and carbohydrate metabolism and inflammation. AKR1C4 has been demonstrated to be a direct target gene of LXR (Stayrook et al., 2008). Thus, AKR1C4 may play a role in LXR-regulated metabolism or inflammation.

OTHERS

AKR1D1 catalyzes the 5β-reduction of bile acid intermediates and steroid hormones which carry a delta (4)-3-one structure. AKR1D1 is expressed in liver, colon, brain, and testis (Charbonneau and The, 2001; Jin et al., 2011). Deficiency of this enzyme may lead to neonatal cholestasis, hepatitis, and liver failure (Barski et al., 2011; Wakasaya et al., 2011). Deletion of AKR6A5 is associated with epilepsy and impairment of learning and memory disorders, inflammation, and carcinogenesis. By far, our understanding of the regulation of human AKRs remains limited. Further investigation of the regulation of human AKRs and AKR's functions under normal and pathological conditional will help develop novel therapeutic approaches for treatment of metabolic disorders, inflammation, cancer, and other relevant diseases.

ACKNOWLEDGMENTS

We apologize to colleagues for not citing their work due to space limitations. This work was supported by grants 1R01HL103227 and 1R15DK088733 from NIH and a Scientist Development Grant 0830255N from the American Heart Association (to Yanqiao Zhang).

REFERENCES

Abdelin, Z., Sen, S., and Field, J. (2012). Aldo-keto reductases protect lung adenocarcinoma cells from the acute toxicity of β[αP]-7,8-trans-dihydriodiol. Chem. Res. Toxicol. 25, 113–121.

Ahmed, M. M., Wang, T., Luo, Y., Ye, S., Wu, Q., Guo, Z., Roeback, B. D., Sutter, T. R., and Yang, J. Y. (2011). Aldo-keto reductase-7A protects liver cells and tissues from acetaminophen-induced oxidative stress and hepatotoxicity. Hepatology 54, 1322–1332.

Barski, O. A., Papusha, V. Z., Kunkel, G. R., and Gabbay, K. H. (2004). Regulation of aldehyde reductase expression by STAF and CHOP. Genomics 83, 119–129.

Barski, O. A., Tippurajah, S. M., and Bhatnagar, A. (2008). The aldo-keto reductase superfamily and its role in drug metabolism and detoxification. Drug Metab. Rev. 40, 553–624.

Birtwistle, J., Hayden, R. E., Khanim, F. L., Green, R. M., Parry, C., Davies, N. J., Wake, N., Schrew, H., Ride, J. P., Chipman, J. K., and Bunce, C. M. (2009). The aldo-keto reductase AKR1C3 contributes to 7,12-dimethylbenz(a)anthracene-3,4-dihydrodiol mediated oxidative DNA damage in myeloid cells: implications for leukemogenesis. Mutat. Res. 662, 67–74.

Burczynski, E. M., Lin, H. K., and Penning, T. M. (1999). Isoform-specific induction of a human aldol reductase by polycyclic aromatic hydrocarbons (PAHs), electrophiles, and oxidative stress: implications for the alternative pathway of PAH activation catalyzed by human dihydriodiol dehydrogenase. Cancer Res. 59, 607–614.

Busolin, G., Malacrida, S., Bisulli, F., Striano, P., Di Bonaventura, C., Egeo, G., Pasini, E., Cianci, V., Ferlazzo, E., Bianchi, A., Coppola, G., Elia, M., Mecarelli, O., Gobbi, G., Casellato, S., Marchini, M., Binelli, S., Ferri, E., Granata, T., Posar, A., Parmeggiani, A., Vigliano, P., Boniver, C., Aguglia, U., Striano, S., Tinuper, P., Giallonardo, A. T., Michelucci, R., and Nobile, C. (2011). Association of intrinsic variants of the KCNAB1 gene with lateral temporal epilepsy. Epilepsy Res. 94, 110–116.

Charbonneau, A., and The, V. L. (2001). Genomic organization of a human 5β-reductase and its pseudogene and substrate selectivity of the expressed enzyme. Biochim. Biophys. Acta 1517, 228–235.

Chen, J. Y., Yuan, C. C., Chow, K. C., Wang, P. H., Lai, C. R., Yen, M. S., and Wang, L. S. (2005). Overexpression of dihydriodiol dehydrogenase is associated with cisplatin-based chemotherapy resistance in ovarian cancer patients. Gynecol. Oncol. 97, 110–117.

Chun, J. Y., Nadiminty, N., Dutt, S., Lou, W., Yang, J. C., Kung, H. J., Evans, C. P., and Gao, A. C. (2009). Interleukin-6 regulates androgen synthesis in prostate cancer cells. Clin. Cancer Res. 15, 4815–4822.

Clayton, P. T. (2011). Disorders of bile acid synthesis. J. Inherit. Metab. Dis. 34, 593–604.

Deng, H. B., Adikari, M., Parekh, H. K., and Simpkins, H. (2004). Ubiquitous induction of resistance to platinum drugs in human ovarian, cervical, germ-cell and lung carcinoma tumor cells overexpressing isofoms 1 and 2 of dihydriodiol dehydrogenase. Cancer Chemother. Pharmacol. 54, 301–307.

Deng, H. B., Parekh, H. K., Chow, K. C., and Simpkins, H. (2002). Increased expression of dihydriodiol dehydrogenase induces resistance to cisplatin in human ovarian carcinoma cells. J. Biol. Chem. 277, 15035–15043.
of dihydroxydiol reductase as a prognostic marker of non-small cell lung cancer. Cancer Res. 61, 2722–2731.

Huang, J. J., Chow, K. C., Wang, H. W., and Wang, L. S. (2006). Expression of dihydroxydiol dehydrogenase and resistance to chemotherapy and radiotherapy in adenocarcinoma cells of lung. Anticancer Res. 26, 2949–2955.

Jez, J. M., Bennett, M. J., Schlegel, B. P., Lewis, M., and Penning, T. M. (1997a). Comparative anatomy of the aldo-keto reductase superfamily. Biochem. J. 326 (Pt 3), 625–636.

Jez, J. M., Flynn, T. N., and Penning, T. M. (1997b). A new nomenclature for the aldo-keto reductase superfamily. Biochem. Pharmacol. 54, 539–644.

Jiang, T., Qu, J. J., Nishinaka, T., and Zhang, N. (2008). Transcription factor Ap-1 regulates TGF-beta(1)-induced expression of aldose reductase in cultured human mesangial cells. Nephron (Carlton) 13, 212–217.

Jin, Y., Mesaros, A. C., Blain, I. A., and Penning, T. M. (2011). Stereospecific reduction of Sbeta-dehydrogenase by human ketosteroid reductases of the AKR (aldo-keto reductase) superfamily: role of AKR1C1-AKR1C4 in the metabolism of testosterone and progesterone via the Sbeta-reductase pathway. Biochem. J. 437, 53–61.

Jin, Y., and Penning, T. M. (2007). Aldo-keto reductases and bioactivation/detoxification. Annu. Rev. Pharmacol. Toxicol. 47, 263–292.

Ko, B. C., Ruepp, B., Bohren, K. M., Gabbay, K. H., and Chung, S. S. (1997). Identification and characterization of multiple osmotic response sequences in the human aldose reductase gene. J. Biol. Chem. 272, 16431–16437.

Kropotova, E. S., Tyshko, R. A., Zinova’ev, O. L., Zyrizanova, A. F., Khankin, S. L., Cherkess, V. L., Aliev, V. A., Beresten, S. F., Oparina, N., and Mashlova, T. D. (2010). Down-regulation of AKR1B10 gene expression in colorectal cancer. Mol. Biol. (Mosk.) 44, 243–250.

Lee, Y. J., Lee, G. J., Baek, B. I., Heo, S. H., Won, S. Y., Im, J. H., Cho, M. K., Nam, H. S., and Lee, S. H. (2011). Cadmium-induced up-regulation of aldo-keto reductase 1C3 expression in human nasal septum carcinoma RPMI-2650 cells: involvement of reactive oxygen species and phosphatidylinositol 3-kinase/Akt. Environ. Toxicol. Pharmacol. 31, 469–478.

Dief-Dacal, B., Gayarre, I., Gharbi, S., Timms, J. F., Coderch, C., Gago, F., and Perez-Sala, D. (2011). Identification of aldo-keto reductase AKR1B10 as a selective target for modification and inhibition by prostaglandin A1(1): implications for antitumoral activity. Cancer Res. 71, 4161–4171.

Ebert, B., Kisiela, M., Wsol, V., and Maser, E. (2011). Proteasome inhibitors MG-132 and bortezomib induce AKR1C1, AKR1C3, AKR1B1, and AKR1B10 in human colon cancer cell lines SW-480 and HT-29. Chem. Biol. Interact. 191, 239–249.

Fantozzi, I., Platoshyn, O., Wong, A. A., Harrison, S., Remillard, C. V., Furtaido, M. R., Petrasukne, O. V., and Vozder, M. N. (2006). Response of progestin-dependent 2 up-regulates expression and function of voltage-gated K+ channels in human pulmonary artery smooth muscle cells. Am. J. Physiol. Lung Cell Mol. Physiol. 291, L993–L1004.

Fung, K. M., Samara, E. N., Wong, C., Metwally, A., Kuhn, R., Bane, B., Liu, C. Z., Yang, J. T., Pitha, J. V., Culkin, D. J., Kropp, B. P., Penning, T. M., and Lin, H. K. (2006). Increased expression of type 3 alpha-hydroxydehydrogenase/type 5 beta-hydroxydehydrogenase (AKR1C3) and its relationship with androgen receptor in prostate carcinoma. Endocr. Relat. Cancer 13, 169–180.

Ge, Y., Xin, L., Ma, H., Li, T., Chiang, J. Y., and Zhang, Y. (2011). Aldo-keto reductase 1B7 is a target gene of FXR and regulates lipid and glucose homeostasis. J. Lipid Res. 52, 1561–1568.

Gonzales, E., Cresteil, D., Bauscan, C., Dabadie, A., Gerhardt, M. F., and Jacqumin, E. (2004). SRD5B1 (AKR1D1) gene analysis in delta(4)-3-oxosteroid 5beta-reductase deficiency: evidence for primary genetic defect. J. Hepatol. 40, 716–718.

Grip, O., Janczaksiene, S., and Lindgren, S. (2002). Atorvastatin activates PPAR-gamma and attenuates the inflammatory response in human monocytes. Inflamm. Res. 51, 58–62.

Hevir, N., Youk, K., Sinkovec, J., Ribic-Pucič, M., and Rizner, T. L. (2011). Aldo-keto reductases AKR1C1, AKR1C2 and AKR1C3 may enhance progestosterone metabolism in ovarian endometriosis. Chem. Biol. Interact. 191, 217–226.

Hsu, N. Y., Ho, H. C., Chow, K. C., Lin, T. Y., Shih, C. S., Wang, L. S., and Tsai, C. M. (2001). Overexpression of
human colon cancer cells resistant to methotrexate: role in the cell cycle and apoptosis. Biochem. Pharmacol. 75, 414–426.

Seo, H. G., Nishinaka, T., and Yabe-Nishimura, C. (2000). Nitric oxide up-regulates aldose reductase expression in rat vascular smooth muscle cells: a potential role for aldose reductase in vascular remodeling. Mol. Pharmacol. 57, 709–717.

Shoeb, M., Yadav, U. C., Srivastava, S. K., and Ramana, K. V. (2011). Inhibition of aldose reductase prevents endotoxin-induced inflammation by regulating the arachidonic acid pathway in murine macrophages. Free Radic. Biol. Med. 51, 1686–1696.

Stanbrough, M., Bubley, G. J., Ross, K., Golub, T. R., Rubin, M. A., Penning, T. M., Febbo, P. G., and Balk, S. P. (2006). Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. Cancer Res. 66, 2815–2825.

Stayrock, K. R., Rogers, P. M., Savkur, R. S., Wang, Y., Su, C., Varga, G., Bu, X., Wei, T., Nagpal, S., Liu, X. S., and Burris, T. P. (2008). Regulation of human 3 alpha-hydroxysteroid dehydrogenase (AKR1C4) expression by the liver X receptor alpha. J. Neurosci. Res. 89, 576–584.

Wang, R., Wang, G., Ricard, M. J., Ferris, B., Strulovici-Barel, Y., Salit, I., Hackett, N. R., Gudas, L. J., and Crystal, R. G. (2010). Smoking-induced upregulation of AKR1B10 expression in the airway epithelium of healthy individuals. Chest 138, 1402–1410.

Yabe-Nishimura, C., Nishinaka, T., Iwata, K., and Seo, H. G. (2003). Up-regulation of aldose reductase by the substrate, methylglyoxal. Chem. Biol. Interact. 143–144, 317–323.

Yang, B., Hodgkinson, A. D., Oates, P. J., Kwon, H. M., Millward, B. A., and Demaine, A. G. (2006). Elevated activity of transcription factor nuclear factor of activated T-cells 5 (NFAT5) and diabetic nephropathy. Diabetes 55, 1450–1455.

Zhang, L., Lee, J. J., Tang, H., Fan, Y. H., Xiao, L., Ren, H., Kurie, J., Morice, R. C., Hong, W. K., and Mao, L. (2008). Impact of smoking cessation on global gene expression in the bronchial epithelium of chronic smokers. Cancer Prev. Res. (Phila.) 1, 112–118.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 30 November 2011; paper pending published: 05 January 2012; accepted: 20 February 2012; published online: 09 March 2012.

Citation: Chen W-D and Zhang Y (2012) Regulation of aldo–keto reductases in human diseases. Front. Pharmacol. 3:35.

doi: 10.3389/fphar.2012.00035

This article was submitted to Frontiers in Experimental Pharmacology and Drug Discovery, a specialty of Frontiers in Pharmacology.

Copyright © 2012 Chen and Zhang. This is an open-access article distributed under the terms of the Creative Commons Attribution Non Commercial License, which permits non-commercial use, distribution, and reproduction in other forums, provided the original authors and source are credited.