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Role of aldo-keto reductases in development of prostate and breast cancer

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1. ABSTRACT

Aldo-keto reductase (AKR) is a super gene family, consisting of fourteen families and more than 40 members overall. These proteins have been well known as metabolic enzymes of carbonyls, but recent data indicates that the members in AKR families 1 and 7 (AKR1 & AKR7) are involved in the development of some human and rodent tumors, such as in primary liver, lung, colorectal, prostate, and breast cancers. They are involved in the pathogenesis, diagnosis, and therapy of these tumors. This manuscript discusses the recent progression in AKR study in mammalian tumors, focusing on prostate and breast cancer.

2. INTRODUCTION

Aldo-keto reductases (AKR) are a large group of carbonyl metabolic enzymes that ubiquitously exist throughout the evolutionary tree, from prokaryotes to eukaryotes, including in humans (1). In the nomenclature system proposed by *the 8th International Workshop on the Enzymology and Molecular Biology of Carbonyl Metabolism*, the root symbol "AKR" stands for aldo-keto reductase; an Arabic number designates the family; a capitol letter indicates the subfamily when multiple subfamilies exist; and another Arabic numeral represents a unique protein in this subfamily. The identity of the amino acid sequences between the families is usually less than 40%, while it is more than 60% among constituent members within a subfamily. Currently, a total of fourteen families have been defined, nine of which consist of multiple subfamilies. The numbering of known members of each subfamily was assigned in an arbitrary fashion, with any new additions to a subfamily being numbered chronologically. More information about the classification of this AKR superfamily is available at the web site: www.med.upenn.edu/akr.

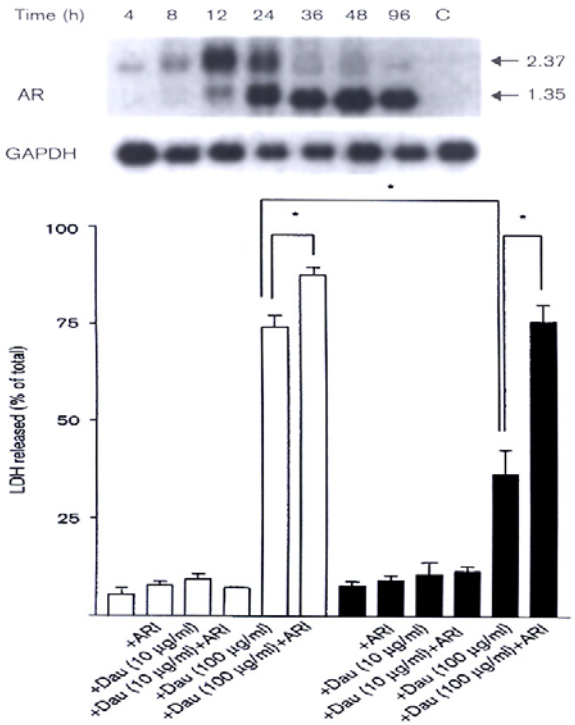

Figure 1. Induction of AR gene expression in HepG2 cells by hypertonic medium (Upper) and its effect on daunorubicin cytotoxicity (Lower). Mature AR mRNA reached the maximal level after 36 hours in hypertonic medium, which resulted in the cell resistance to daunorubicin. This resistance was efficiently reversed by AR inhibitor (ARI). Hypertonic medium and ARI both had no effect on cell growth (22).

All members of the AKR superfamily are monomeric cytoplasmic proteins, involved in carbonyl metabolism with NADPH as cofactor (2). Most of AKR members have a wide range of substrate specificity, catalyzing the NADPH-dependent reduction of various xenobiotics and endogenous carbonyls, such as aldehydes and ketones, making them involved in detoxification processes of living cells (3). Increasing evidence indicates that some members of the AKR superfamily are involved in carcinogenic processes, affecting tumor formation and development, as well as therapeutics and prognosis. Of the fourteen families, families AKR1, AKR6, and AKR7 are identified in mammalian species, but proteins in the family AKR6 are beta-subunits of the shaker-related voltage-gated K^+ channels isolated from humans, rats, and cows. Currently, research shows that AKR1 and AKR7 members are related to pathogenesis and therapy of tumors in mammalians (4, 5). This review will focus on recent advances on the aldo-keto reductases (AKR1 and AKR7) that are involved in the development of mammalian tumors, with focus on prostate and breast cancers.

3. MAMMALIAN AKR1 AND AKR7 FAMILIES

3.1. Aldo-keto reductase family 1

Aldo-keto reductase family 1 (AKR1) is one of the largest families in the AKR superfamily, composed of four subfamilies: aldehyde reductases (AKR1A1-3), aldose reductases (AKR1B1-11), hydroxysteroid dehydrogenases (AKR1C1-17), and steroid reductases (AKR1D1-3) (2). An additional member, AKR1E1, identified in mice, has similar genomic organization to aldose reductase (AKR1B) (6, 7). The enzymes in this family carry out a wide range of biological and pathological functions, including carbonyl detoxification, osmolytic regulation, hormonal metabolism, diabetic complications, and tumor development (8-16).

The involvement of AKR in mammalian tumor development and therapy is a novel research topic. Zeindl-Eberhart and colleagues first reported the induction of rat aldose reductase (AR) in rat hepatomas (17, 18). Takahashi's work confirmed this finding and further unraveled that the increased AR protein rendered rat hepatoma cells resistant to the carbonyl damages induced by 3-deoxyglucosone and glyceraldehyde. This suggests that AR protects rat hepatoma cells from harmful carbonyl metabolites, produced by rapidly growing cancer cells (19). In a subsequent study, this group further revealed that the expression of aldose reductase was marked in cancerous lesions in hepatoma-bearing LEC (Long-Evans with a cinnamon-like color) rat liver, compared to normal surrounding tissues (20). These results indicated that overexpression of AR in hepatocarcinogenesis may be related to the acquisition of immortality of the cancer cells, by detoxifying cytotoxic carbonyls.

In humans, Cao, *et al.* (21) reported for the first time the overexpression of human AR in hepatocellular carcinomas (HCC). They observed 24 human HCC surgical specimens and found that AR was overexpressed in about 29% of the cancerous tissues, compared to normal surrounding tissues. By stimulating the expression of AR in HepG2, a human HCC cell line, with hypertonic medium, this group further revealed that AR conferred the cancerous cells resistant to daunorubicin, an antitumor agent (Figure 1) (22). The mechanisms of the AR re-expression and the cause-effect relationship between AR induction and hepatocarcinogenesis remain unclear. Nevertheless, this finding will aid in improving chemotherapy strategies and the development of new drugs for the treatment of this disease. It will be important to further understand the correlation between AR expression and the tumor type, grade, and differentiation status.

The investigation of AR expression in HCC tissues has led to the discovery of a novel member of AKR1 family, designated aldose reductase-like-1 (ARL-1) due to its resemblance in amino acid sequence to that of human aldose reductase (21). In the nomenclature system, this protein is sequentially named aldo-keto reductase family 1 member B 10 (AKR1B10). This gene was overexpressed in approximately 54% of human HCC specimens (Figure 2), according to Cao *et al.*, which was confirmed by two independent groups (23, 24).

Recently, Fukumoto, *et al.* (25) reported the overexpression of ARL-1 in 84.4% of human lung squamous cell carcinomas (SCC) and 29.2% of adenocarcinomas in smokers, proposing this protein as a

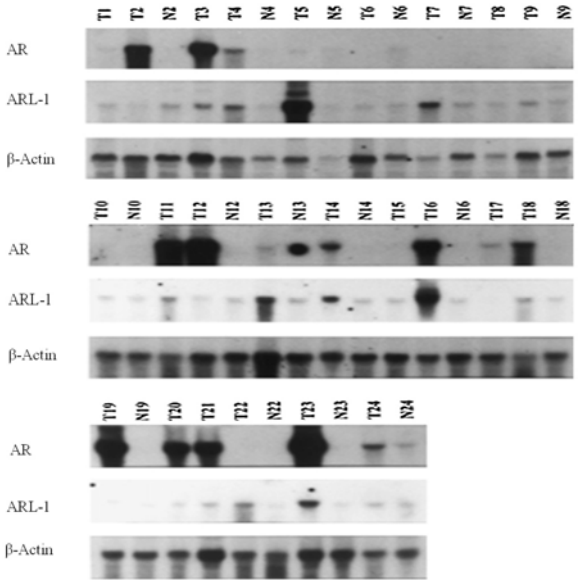

Figure 2. Expression of AR and ARL-1 in HCC tissues. 20μg of total RNAs from tumor tissues (T) and surrounding normal tissues (N) were used and hybridized with AR and ARL-1 cDNAs. The amounts and quality of RNA loaded were assessed by β–actin cDNA probe (21).

potential marker of lung cancer. Multiple regression analysis identified that smoking was an independent variable responsible for the overexpression of ARL-1 in these lung cancer tissues, indicating the role of this protein in the activation of hydrocarbons present in tobacco smoke. This was supported by the overexpression of ARL-1 in precancerous lesions, squamous metaplasia, of the lung. However, another potential mechanism was proposed by Penning, in which increased ARL-1 expression may lead to depletion of the retinoic acid precursor, retinal, thus downregulating the retinoic acid pathway (1). Retinoic acid pathway plays an important role in cell differentiation (26).

3.2. Aldo-keto reductase family 7

Aldo-keto reductase family 7 (AKR7) is composed of aflatoxin B1 aldehyde reductases (AFB1-AR). In the nomenclature system, this family belongs to AKR7A, consisting of 5 members, AKR7A1-5. These enzymes are involved in the detoxification of the aldehyde metabolites of aflatoxin B1, a carcinogen. Aflatoxin B1 (AFB1) is a potent hepatocarcinogen produced by *Aspergillus flavus*, a mold that contaminates rice and cereal crops in humid environments (27). The aflatoxin B1 aldehyde metabolites, such as dihydrodiol, contribute to the cytotoxicity and genotoxicity of this hepatocarcinogen, by forming protein or DNA adducts (28). AFB1-ARs can convert the dihydrodiol to a less reactive dialcohol, protecting hepatocytes from aflatoxin B1 carcinogenic toxicity (29).

AFB1-ARs are also NADPH-dependent reductases. Five AFB1-AR isoforms have been identified, designated AKR7A1-5. AKR7A1 and AKR7A4 were isolated from the rat liver; AKR7A2 and AKR7A3 from the human liver; and AKR7A5 from the mouse liver (30). These enzymes can efficiently convert the AFB1 dihydrodiol to its dialcohol, a less active form. Structurally, these AKR7A proteins are predicted to possess distinct secondary structural features that distinguish them from the prototypic AKR1 family, but the catalytic- and NADPH-binding residues appear to be conserved in both families. In addition, certain predicted structural features of the AKR7 family are shared with the AKR6 beta-subunits of voltage-gated K^+-channels (31).

AKR7A1 was isolated by Judah, *et al.* from a cytosolic fraction prepared from the rat liver bearing pre-neoplastic lesions and experiencing treatment with the anti-oxidant ethoxyquin (32). This enzyme can catalyze aflatoxin B1-dihydrodiol to aflatoxin B1-dialcohol, a less active form. The AKR7A1 gene was cloned by Ellis and colleagues from a rat's liver, with the mRNA coding for this enzyme was remarkably elevated when an ethoxyquin-containing diet was fed, coupled with acquisition of resistance to AFB1 (33). The human homologues, AKR7A2 and AKR7A3, were isolated by Ireland's and Knight's groups, respectively (28, 31). AKR7A2 was 78% identical to AKR7A1. Unlike its rat homologue, however, AKR7A2 is constitutively expressed in the human liver, and in a wide range of extra-hepatic tissues. In addition to the aflatoxin B1-8, 9-dihydrodiol, AKR7A2 shows high affinity and activity to 2-carboxybenzaldehyde (2-CBA) and the structurally related gamma-aminobutyric acid metabolite, succinic semialdehyde (SSA). Another human homologue, AKR7A3, shows 80% and 88% amino acid sequence identity to rat AKR7A1 and human AKR7A2, respectively. AKR7A3 also exhibits higher efficiency in catalyzing AFB1 dihydrodiol reduction (pH 7.4), than the other enzymes, such as cytochrome P450s and glutathione S-transferases (28).

Unlike the aflatoxin B1-dihydrodiol, the dialcohol does not bind to proteins or DNA. The presence of these enzymes in hepatic cells, therefore, confers the cells' resistance to carcinogenesis caused by aflatoxin B1, indicating a mechanistic role of AFB1-AR in hepatocarcinogenesis of aflatoxin B1. A large number of compounds can confer the hepatocytes resistance to aflatoxin B1 hepatocarcinogenesis in the rat mode through the induction of AFB1-AR expression. These compounds include phytochemicals [benzyl isothiocyanate, coumarin (CMRN), and indole-3-carbinol], and synthetic antioxidants and other agents (butylated hydroxyanisole, diethyl maleate, ethoxyquin, beta-naphthoflavone, oltipraz, phenobarbital, or trans-stilbene oxide). Therefore, the role of AKR7A enzymes in chemoprevention was attributed to their upregulation induced by these chemopreventive agents (14, 33-36). For instance, Hayes and Sutter groups reported that rat hepatic AFB1-AR levels were induced 20-, 15-, 9-, and 6-fold, respectively by 1,2-dithiole-3-thione (D3T), ethoxyquin, butylated hydroxyanisole, and oltipraz (37, 38). In these rats, phenobarbital or 3-methylcholanthrene also induced approximate 1.4-fold increase of liver AFB1-AR.

In addition to the increased expression of AFB1-AR in the livers of rats that were fed these

chemopreventors, interestingly, Mcleod, *et al.* (29) found that hepatic cytosol of selenium (a co-factor of antioxidant enzyme glutathione peroxidase)-deficient Fischer 344 rats possessed remarkable increased AFB1-AR protein levels and enzyme activity. Furthermore, Fischer 344 rats that were fed a diet deficient in selenium were more resistant to the hepatocarcinogenic effect of aflatoxin B1 than those fed with a selenium-sufficient diet. However, the molecular mechanisms remain to be elucidated.

4. ALDO-KETO REDUCTASES AND PROSTATE CANCER

In vitro studies indicate that the human AKR1C subfamily functions as 3-keto-, 17-keto-, and 20-ketosteroid reductases or as 3-alpha-, 17-beta-, and 20-alpha-hydroxysteroid oxidases, thus involved in the metabolism of these ketosteroids and hydroxysteroids (39-43). For instance, 20-alpha-hydroxysteroid is the substrate of human 20-alpha-hydroxysteroid dehydrogenases (AKR1C1). 3-alpha- and 17-beta-hydroxysteroid can be oxidized by 3 alpha-hydroxysteroid dehydrogenase type 3 (AKR1C2). In addition, 17-beta-hydroxysteroid is also the substrate of AKR1C3, and 3-alpha-hydroxysteroid can be metabolized by 3-alpha-hydroxysteroid dehydrogenase type 1 (AKR1C4). In steroid target tissues, 3-alpha-hydroxysteroid dehydrogenases possess enzymatic activity to 5-alpha-dihydrotestosterone, a potent androgen implicated in benign prostate hyperplasia and prostate cancer, indicating the involvement of AKR1Cs in prostate carcinogenesis (44). Moreover, AKR1C isozymes are associated with pre-receptor regulation of steroid receptors, nuclear orphan receptors, and membrane-bound ligand-gated ion channels (45). In concert with short-chain dehydrogenases/reductases, these AKR1C members act as switches to control ligand access to nuclear receptors (45). The pluripotency of these enzymes' functions confers their role in steroid metabolism and ligand-receptor interactions, indicating their roles in tumorigenesis within the prostate and other steroid-targeted organs (46).

Human AKR1C3 has two isoforms, 3-alpha-hydroxysteroid dehydrogenase and 17-beta-hydroxysteroid dehydrogenase. 17-beta-hydroxysteroid dehydrogenase was identified within the human prostate and has high identity in its amino acid sequence to that of 3-alpha-hydroxysteroid dehydrogenase. Human AKR1C3 can catalyze the reduction of Delta (4)-androstene-3, 17-dione into testosterone; 5-alpha-dihydrotestosterone into 3-alpha- and 3-beta-androstanediol; and estrone into 17 beta-estradiol. Within the prostate, AKR1C3 favors the formation of inactive androgens (47).

Nishi, *et al* (48) isolated a novel member of AKR superfamily from androgen-stimulated rat prostate cells. The expression of this gene was induced by androgen, and thus designated androgen-inducible aldehyde reductase (AIAR). AIAR exhibits 80% amino acid sequence identity to that of rat aflatoxin B1 aldehyde reductase, but possesses only 16% of the enzyme activity to 4-nitrobenzaldehyde, indicating a difference in substrate specificity. Although the physiological substrate(s) of AIAR has not been identified, its inducibility by androgen suggests that AIAR may associate with some growth-related processes in the rat prostate.

Using real-time PCR, Ji, *et al.* (49) investigated the expression profiles of human AKR1C subfamily in prostate cancer and surrounding normal tissues. In this study, they found that AKR1C2 expression was reduced in approximately half of the cancerous tissues, while AKR1C3 and AKR1C4 expressions were not significantly altered. In cell lines derived from the human prostate, a high expression of AKR1C2 was also detected in the cancerous cells, but not in normal cells (50). It was reported that in prostate cells AKR1C2 acts as a 3-ketosteroid reductase, eliminating 5-alpha-dihydrotestosterone (5-alpha-DHT), and preventing the activation of the androgen receptor (50, 51). However, additional studies are needed to further define the significance of reduced AKR1C2 expression in prostate cancer and its role in modulating the local availability of 5-alpha-DHT.

AKR1C3 is mainly expressed in the human prostate and mammary gland. In a normal prostate, AKR1C3 is expressed in stromal cells and at a low level in epithelial cells. In adenocarcinoma of the prostate, however, AKR1C3 expression was elevated in the endothelial and cancerous cells (47). It is noteworthy to state that in the investigation of this gene a precaution should be taken to avoid false results, due to the high sequence identity (>86%) to other members (AKR1C1, AKR1C2 and AKR1C4) (52).

5. ALDO-KETO REDUCTASES AND BREAST CANCER

The receptor tyrosine kinase ErbB2 (HER-2/neu) is overexpressed in up to 30% of breast cancers, and is associated with poor prognosis and high metastatic rates, especially in node-positive tumors (53, 54). In the investigation of the molecular mechanisms, Zhang, *et al.* found that AKR1C2 was upregulated in HER-2 positive breast tumors, aiding in cancerous cell growth via detoxification (55).

Mammographic density is identified as a strong risk factor for breast cancer. Identifying genetic variants causing mammographic density in hormone users is important in understanding hormonal carcinogenesis in the breast (56). In a comparative study on hormone consumption patients, Lord *et al.* reported a potential correlation between the AKR1C4 expression and mammographic density due to the involvement of AKR1C4 in progesterone metabolism (57). Recently, Lewis, *et al.* confirmed the changes in the expression of progesterone metabolic enzymes in human breast carcinoma (58). They found that the expression of SRD5A1 (5-alpha-reductase type 1) and SRD5A2 (5-alpha-reductase type 2) was elevated, while the expression of AKR1C1, AKR1C2 and AKR1C3 was reduced in tumors, as compared to normal breast tissue. The changes in progesterone metabolizing enzymes expression help explain the increases in

mitogen/metastasis inducing 5alphaP (5-alpha-pregnane-3, 20-dione) and decreases in mitogen/metastasis inhibiting 3alphaHP (4-pregnen-3-alpha-ol-20-one) progesterone metabolites found in breast tumor tissues. Understanding what causes these changes in expression could help in designing protocols to prevent or reverse the changes in progesterone metabolism associated with breast cancer (58). However, a further molecular and mechanistic study, obviously, is required to elucidate the role of AKR members in pathogenesis and prognosis of breast cancer.

6. SUMMARY AND PERSPECTIVE

AKR members are widely involved in various aspects of human and rodent cancer, including the pathogenesis, prevention, chemotherapy, and prognosis. The roles and mechanisms vary with AKR members and /or tumor types. It is significant to elucidate their roles in tumorigenesis, as well as their effects on the therapeutics and prognosis of human cancers. Due to the complexity of etiology and pathogenesis of human cancer and the differences among each member of AKR superfamily in their physical and chemical properties, and substrate specificity, it is still a long journey to fully understand this research topic. A systemic observation of the molecular behavioral of these proteins in human tumor tissues and an extensive investigation of their mechanisms within human cells and/or animal models will help acquire further insights to benefit cancer patients.

7. REFERENCES

1. Penning, T. M.: AKR1B10: a new diagnostic marker of non-small cell lung carcinoma in smokers. *Clin Cancer Res* 11, 1687-90 (2005)
2. Jez, J. M., T. G. Flynn & T. M. Penning: A new nomenclature for the aldo-keto reductase superfamily. *Biochem Pharmacol* 54, 639-47 (1997)
3. Forrest, G. L. & B. Gonzalez: Carbonyl reductase. *Chem Biol Interact* 129, 21-40 (2000)
4. Kawai, K., M. Jijiwa, Y. Shimono, K. Kurokawa, Y. Murakumo, M. Ichihara & M. Takahashi: Establishment and characterization of mouse mammary carcinoma cell lines expressing RET with a multiple endocrine neoplasia 2A mutation. *Cancer Sci* 94, 992-7 (2003)
5. Zeindl-Eberhart, E., S. Klugbauer, N. Dimitrijevic, P. R. Jungblut, S. Lamer & H. M. Rabes: Proteome analysis of rat hepatomas: carcinogen-dependent tumor-associated protein variants. *Electrophoresis* 22, 3009-18 (2001)
6. Bohren, K. M., O. A. Barski & K. H. Gabbay: Characterization of a novel murine aldo-keto reductase. *Adv Exp Med Biol* 414, 455-64 (1997)
7. Vergnes, L., J. Phan, A. Stolz & K. Reue: A cluster of eight hydroxysteroid dehydrogenase genes belonging to the aldo-keto reductase supergene family on mouse chromosome 13. *J Lipid Res* 44, 503-11 (2003)
8. Kaneko, M., L. Bucciarelli, Y. C. Hwang, L. Lee, S. F. Yan, A. M. Schmidt & R. Ramasamy: Aldose reductase and AGE-RAGE pathways: key players in myocardial ischemic injury. *Ann N Y Acad Sci* 1043, 702-9 (2005)
9. Srivastava, S. K., K. V. Ramana & A. Bhatnagar: Role of aldose reductase and oxidative damage in diabetes and the consequent potential for therapeutic options. *Endocr Rev* 26, 380-92 (2005)
10. Petrash, J. M.: All in the family: aldose reductase and closely related aldo-keto reductases. *Cell Mol Life Sci* 32, 737-49 (2004).
11. Burg, M. B.: Molecular basis of osmotic regulation. *Am J Physiol* 268, F983-96 (1995)
12. Grimshaw, C. E.: Aldose reductase: model for a new paradigm of enzymic perfection in detoxification catalysts. *Biochemistry* 31, 10139-45 (1992)
13. Licht, T., F. Herrmann, M. M. Gottesman & I. Pastan: *In vivo* drug-selectable genes: a new concept in gene therapy. *Stem Cells* 15, 104-11 (1997)
14. Hayes, J. D., R. McLeod, E. M. Ellis, D. J. Pulford, L. S. Ireland, L. I. McLellan, D. J. Judah, M. M. Manson & G. E. Neal: Regulation of glutathione S-transferases and aldehyde reductase by chemoprotectors: studies of mechanisms responsible for inducible resistance to aflatoxin B1. *IARC Sci Publ* 175-87 (1996)
15. Steckelbroeck, S., Y. Jin, S. Gopishetty, B. Oyesanmi & T. M. Penning: Human cytosolic 3alpha-hydroxysteroid dehydrogenases of the aldo-keto reductase superfamily display significant 3beta-hydroxysteroid dehydrogenase activity: implications for steroid hormone metabolism and action. *J Biol Chem* 279, 10784-95 (2004)
16. Yasuda, N., K. Fujino, T. Shiraji, F. Nambu & K. Kondo: Effects of steroid 5alpha-reductase inhibitor ONO-9302 and anti-androgen allylestrenol on the prostatic growth, and plasma and prostatic hormone levels in rats. *Jpn J Pharmacol* 74, 243-52 (1997)
17. Zeindl-Eberhart, E., P. R. Jungblut, A. Otto & H. M. Rabes: Identification of tumor-associated protein variants during rat hepatocarcinogenesis. Aldose reductase. *J Biol Chem* 269, 14589-94 (1994)
18. Zeindl-Eberhart, E., P. Jungblut & H. M. Rabes: Expression of tumor-associated protein variants in chemically induced rat hepatomas and transformed rat liver cell lines determined by two-dimensional electrophoresis. *Electrophoresis* 15, 372-81 (1994)
19. Takahashi, M., J. Fujii, E. Miyoshi, A. Hoshi & N. Taniguchi: Elevation of aldose reductase gene expression in rat primary hepatoma and hepatoma cell lines: implication in detoxification of cytotoxic aldehydes. *Int J Cancer* 62, 749-54 (1995)
20. Takahashi, M., A. Hoshi, J. Fujii, E. Miyoshi, T. Kasahara, K. Suzuki, K. Aozasa & N. Taniguchi: Induction of aldose reductase gene expression in LEC rats during the development of the hereditary hepatitis and hepatoma. *Jpn J Cancer Res* 87, 337-41 (1996)
21. Cao, D., S. T. Fan & S. S. Chung: Identification and characterization of a novel human aldose reductase-like gene. *J Biol Chem* 273, 11429-35 (1998)
22. Lee, K. W., B. C. Ko, Z. Jiang, D. Cao & S. S. Chung: Overexpression of aldose reductase in liver cancers may contribute to drug resistance. *Anticancer Drugs* 12, 129-32 (2001)
23. Zeindl-Eberhart, E., S. Haraida, S. Liebmann, P. R. Jungblut, S. Lamer, D. Mayer, G. Jager, S. Chung & H. M. Rabes: Detection and identification of tumor-associated protein variants in human hepatocellular carcinomas. *Hepatology* 39, 540-9 (2004)

24. Scuric, Z., S. C. Stain, W. F. Anderson & J. J. Hwang: New member of aldose reductase family proteins overexpressed in human hepatocellular carcinoma. *Hepatology* 27, 943-50 (1998)
25. Fukumoto, S., N. Yamauchi, H. Moriguchi, Y. Hippo, A. Watanabe, J. Shibahara, H. Taniguchi, S. Ishikawa, H. Ito, S. Yamamoto, H. Iwanari, M. Hironaka, Y. Ishikawa, T. Niki, Y. Sohara, T. Kodama, M. Nishimura, M. Fukayama, H. Dosaka-Akita & H. Aburatani: Overexpression of the aldo-keto reductase family protein AKR1B10 is highly correlated with smokers' non-small cell lung carcinomas. *Clin Cancer Res* 11, 1776-85 (2005)
26. Chambon, P.: A decade of molecular biology of retinoic acid receptors. *Faseb J* 10, 940-54 (1996)
27. Eaton, D. L. & E. P. Gallagher: Mechanisms of aflatoxin carcinogenesis. *Annu Rev Pharmacol Toxicol* 34, 135-72 (1994)
28. Knight, L. P., T. Primiano, J. D. Groopman, T. W. Kensler & T. R. Sutter: cDNA cloning, expression and activity of a second human aflatoxin B1-metabolizing member of the aldo-keto reductase superfamily, AKR7A3. *Carcinogenesis* 20, 1215-23 (1999)
29. McLeod, R., E. M. Ellis, J. R. Arthur, G. E. Neal, D. J. Judah, M. M. Manson & J. D. Hayes: Protection conferred by selenium deficiency against aflatoxin B1 in the rat is associated with the hepatic expression of an aldo-keto reductase and a glutathione S-transferase subunit that metabolize the mycotoxin. *Cancer Res* 57, 4257-66 (1997)
30. Hinshelwood, A., G. McGarvie & E. Ellis: Characterisation of a novel mouse liver aldo-keto reductase AKR7A5. *FEBS Lett* 523, 213-8 (2002)
31. Ireland, L. S., D. J. Harrison, G. E. Neal & J. D. Hayes: Molecular cloning, expression and catalytic activity of a human AKR7 member of the aldo-keto reductase superfamily: evidence that the major 2-carboxybenzaldehyde reductase from human liver is a homologue of rat aflatoxin B1-aldehyde reductase. *Biochem J* 332, 21-34 (1998)
32. Judah, D. J., J. D. Hayes, J. C. Yang, L. Y. Lian, G. C. Roberts, P. B. Farmer, J. H. Lamb & G. E. Neal: A novel aldehyde reductase with activity towards a metabolite of aflatoxin B1 is expressed in rat liver during carcinogenesis and following the administration of an anti-oxidant. *Biochem J* 292, 13-8 (1993)
33. Ellis, E. M., D. J. Judah, G. E. Neal & J. D. Hayes: An ethoxyquin-inducible aldehyde reductase from rat liver that metabolizes aflatoxin B1 defines a subfamily of aldo-keto reductases. *Proc Natl Acad Sci U S A* 90, 10350-4 (1993)
34. Hayes, J. D., D. J. Judah, L. I. McLellan, L. A. Kerr, S. D. Peacock & G. E. Neal: Ethoxyquin-induced resistance to aflatoxin B1 in the rat is associated with the expression of a novel alpha-class glutathione S-transferase subunit, Yc2, which possesses high catalytic activity for aflatoxin B1-8,9-epoxide. *Biochem J* 279, 385-98 (1991)
35. Hayes, J. D., D. J. Judah & G. E. Neal: Resistance to aflatoxin B1 is associated with the expression of a novel aldo-keto reductase which has catalytic activity towards a cytotoxic aldehyde-containing metabolite of the toxin. *Cancer Res* 53, 3887-94 (1993)
36. Kelly, V. P., E. M. Ellis, M. M. Manson, S. A. Chanas, G. J. Moffat, R. McLeod, D. J. Judah, G. E. Neal & J. D. Hayes: Chemoprevention of aflatoxin B1 hepatocarcinogenesis by coumarin, a natural benzopyrone that is a potent inducer of aflatoxin B1-aldehyde reductase, the glutathione S-transferase A5 and P1 subunits, and NAD(P)H:quinone oxidoreductase in rat liver. *Cancer Res* 60, 957-69 (2000)
37. Ellis, E. M., D. J. Judah, G. E. Neal, T. O'Connor & J. D. Hayes: Regulation of carbonyl-reducing enzymes in rat liver by chemoprotectors. *Cancer Res* 56, 2758-66 (1996)
38. Primiano, T., J. A. Gastel, T. W. Kensler & T. R. Sutter: Isolation of cDNAs representing dithiolethione-responsive genes. *Carcinogenesis* 17, 2297-303 (1996)
39. Lin, H. K., J. M. Jez, B. P. Schlegel, D. M. Peehl, J. A. Pachter & T. M. Penning: Expression and characterization of recombinant type 2 3 alpha-hydroxysteroid dehydrogenase (HSD) from human prostate: demonstration of bifunctional 3 alpha/17 beta-HSD activity and cellular distribution. *Mol Endocrinol* 11, 1971-84 (1997)
40. Dufort, I., F. Labrie & V. Luu-The: Human types 1 and 3 3 alpha-hydroxysteroid dehydrogenases: differential lability and tissue distribution. *J Clin Endocrinol Metab* 86, 841-6 (2001)
41. Dufort, I., P. Rheault, X. F. Huang, P. Soucy & V. Luu-The: Characteristics of a highly labile human type 5 17beta-hydroxysteroid dehydrogenase. *Endocrinology* 140, 568-74 (1999)
42. Khanna, M., K. N. Qin, R. W. Wang & K. C. Cheng: Substrate specificity, gene structure, and tissue-specific distribution of multiple human 3 alpha-hydroxysteroid dehydrogenases. *J Biol Chem* 270, 20162-8 (1995)
43. Deyashiki, Y., A. Ogasawara, T. Nakayama, M. Nakanishi, Y. Miyabe, K. Sato & A. Hara: Molecular cloning of two human liver 3 alpha-hydroxysteroid/dihydrodiol dehydrogenase isoenzymes that are identical with chlordecone reductase and bile-acid binder. *Biochem J* 299, 545-52 (1994)
44. Bennett, M. J., R. H. Albert, J. M. Jez, H. Ma, T. M. Penning & M. Lewis: Steroid recognition and regulation of hormone action: crystal structure of testosterone and NADP+ bound to 3 alpha-hydroxysteroid/dihydrodiol dehydrogenase. *Structure* 5, 799-812 (1997)
45. Bauman, D. R., S. Steckelbroeck & T. M. Penning: The roles of aldo-keto reductases in steroid hormone action. *Drug News Perspect* 17, 563-78 (2004)
46. Penning, T. M., Y. Jin, S. Steckelbroeck, T. Lanisnik Rizner & M. Lewis: Structure-function of human 3 alpha-hydroxysteroid dehydrogenases: genes and proteins. *Mol Cell Endocrinol* 215, 63-72 (2004)
47. Lin, H. K., S. Steckelbroeck, K. M. Fung, A. N. Jones & T. M. Penning: Characterization of a monoclonal antibody for human aldo-keto reductase AKR1C3 (type 2 3alpha-hydroxysteroid dehydrogenase/type 5 17beta-hydroxysteroid dehydrogenase); immunohistochemical detection in breast and prostate. *Steroids* 69, 795-801 (2004)
48. Nishi, N., H. Shoji, H. Miyanaka & T. Nakamura: Androgen-regulated expression of a novel member of the aldo-keto reductase superfamily in regrowing rat prostate. *Endocrinology* 141, 3194-9 (2000)
49. Ji, Q., L. Chang, D. VanDenBerg, F. Z. Stanczyk & A. Stolz: Selective reduction of AKR1C2 in prostate cancer and its role in DHT metabolism. *Prostate* 54, 275-89 (2003)

50. Rizner, T. L., H. K. Lin, D. M. Peehl, S. Steckelbroeck, D. R. Bauman & T. M. Penning: Human type 3 3alpha-hydroxysteroid dehydrogenase (aldo-keto reductase 1C2) and androgen metabolism in prostate cells. *Endocrinology* 144, 2922-32 (2003)
51. Rizner, T. L., H. K. Lin & T. M. Penning: Role of human type 3 3alpha-hydroxysteroid dehydrogenase (AKR1C2) in androgen metabolism of prostate cancer cells. *Chem Biol Interact* 143-144, 401-9 (2003)
52. Penning, T. M., M. E. Burczynski, J. M. Jez, C. F. Hung, H. K. Lin, H. Ma, M. Moore, N. Palackal & K. Ratnam: Human 3alpha-hydroxysteroid dehydrogenase isoforms (AKR1C1-AKR1C4) of the aldo-keto reductase superfamily: functional plasticity and tissue distribution reveals roles in the inactivation and formation of male and female sex hormones. *Biochem J* 351, 67-77 (2000)
53. Supanaranond, K., S. Sukarayodhin, M. Tanyakaset, K. Balachandra, D. Jullaksorn, M. Rienkijkarn, N. Hoisanka & S. Tantivanich: The significance of HER-2/neu/c-erbB-2 gene amplification in benign and malignant breast disease. *Southeast Asian J Trop Med Public Health* 28, 631-40 (1997)
54. Fehm, T., P. Maimonis, S. Weitz, Y. Teramoto, A. Katalinic & W. Jager: Influence of circulating c-erbB-2 serum protein on response to adjuvant chemotherapy in node-positive breast cancer patients. *Breast Cancer Res Treat* 43, 87-95 (1997)
55. Zhang, D. H., L. K. Tai, L. L. Wong, L. L. Chiu, S. K. Sethi & E. S. Koay: Proteomics study reveals that proteins involved in metabolic and detoxification pathways are highly expressed in HER-2/neu positive breast cancer. *Mol Cell Proteomics* 4, 1686-1696 (2005)
56. Haiman, C. A., S. E. Hankinson, I. De Vivo, C. Guillemette, N. Ishibe, D. J. Hunter & C. Byrne: Polymorphisms in steroid hormone pathway genes and mammographic density. *Breast Cancer Res Treat* 77, 27-36 (2003)
57. Lord, S. J., W. J. Mack, D. Van Den Berg, M. C. Pike, S. A. Ingles, C. A. Haiman, W. Wang, Y. R. Parisky, H. N. Hodis & G. Ursin: Polymorphisms in genes involved in estrogen and progesterone metabolism and mammographic density changes in women randomized to postmenopausal hormone therapy: results from a pilot study. *Breast Cancer Res* 7, R336-44 (2005)
58. Lewis, M. J., J. P. Wiebe & J. G. Heathcote: Expression of progesterone metabolizing enzyme genes (AKR1C1, AKR1C2, AKR1C3, SRD5A1, SRD5A2) is altered in human breast carcinoma. *BMC Cancer* 4, 27-35 (2004)

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