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Roles of *AKR1C3* in malignancy

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The superfamily of aldo-keto reductases (*AKRs*) is composed of over 190 members and can be classified into 16 different families (visit www.med.upenn.edu/akr). *AKR1C3* (C3 subtype of aldosterone reductase family 1) refers to the first *AKR* in family 1, subfamily C, and is encoded by the *AKR1C3* gene. *AKR1C3* was first cloned and expressed from a human prostate cDNA library. This protein is a soluble monomeric NADP(H) (nicotinamide-adenine dinucleotide phosphate or reduced form of nicotinamide adenine dinucleotide phosphate) dependent oxidoreductase. The *AKR* proteins exhibit at least 40% sequence identity at the amino acid level and have an (α/β) 8-barrel structure within their structure. Especially, *AKR1C3* has 86% sequence identity with *AKR1C1*, *AKR1C2*, and *AKR1C4* [Supplementary Figure 1, http://links.lww.com/CM9/A460]. *AKR1C3* is known to be involved in the metabolism and biosynthesis of estrogen, androgen, progesterone, and prostaglandin, etc.[1]

In a previous study, Wang *et al*[2] demonstrated that *AKR1C2* and *AKR1C3* mediated the transformation of prostaglandin D2 (PGD2) to prostaglandin F2 (PGDF2), and then enhanced the proliferation of prostate cells *via* the activation of G-protein-coupled receptors for prostaglandin F2α (PGF2α) and phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt) signaling pathway. The overexpression of *AKR1C3* is known to clear reactive oxygen species (ROS) and facilitate the accumulation of PGF2α. This not only resulted in the proliferation of prostate cancer (PCa) cells but also facilitated the resistance of PCa cells to radiation by activating the mitogen-activated protein kinase (MAPK) signaling pathway [resulting in the up-regulation of p-MEK (phosphorylated mitogen-activated protein/extracellular signal-regulated kinase) and p-ERK (extracellular signal-regulated kinase) 1/2] and by reducing the expression of peroxisome proliferator-activated receptor γ (PPARγ).[3] Moreover, the ETS-related gene (*ERG*) transcription factor is known to regulate the expression of *AKR1C3* in PCa cells by directly combining with the *AKR1C3* gene. ERG can promote cell migration and invasion, de-differentiation, epithelial-to-mesenchymal transition (EMT), and androgen receptor signal transduction. A recent study also found that the nuclear receptor, estrogen-related receptor alpha (ERRα) can regulate the expression of *AKR1C3* and that both ERRα and *ERG* can synergistically regulate each other at the transcriptional level to promote the advanced growth of PCa.[4]

As a critical androgen synthase, *AKR1C3* promotes the biosynthesis of androgens and the activation of androgen receptors in PCa. Wang *et al*[5] discovered that the *AKR1C3* gene is overexpressed in most aggressive PCa cell lines. *AKR1C3* is known to induce an EMT phenotype in PCa cells both, *in vitro* and *in vivo*, by activating extracellular-regulated protein kinases (ERK) which then up-regulates various transcription factors zinc finger box-binding homeobox 1 (ZEB1), Twist family BHLHT transcription factor 1 (Twist1), and Slug. Some studies reported that a single-nucleotide polymorphism (SNP) in the *AKR1C3* is responsible for the deterioration of PCa. The polymorphism of *AKR1C3* has also been associated with serum testosterone levels during androgen deprivation therapy (ADT) and may represent a prognostic factor for the progression to castration-resistant PCa in Japanese men with metastatic PCa.[6]

An increase in the levels of *AKR1C3* can contribute to the transformation of PGD2 to 11b-PGF2α; this facilitates the activation of proliferative transcription factors such as nuclear factor kappa-B (NF-κB) complex.[3] Studies have also illustrated that the overexpression of *AKR1C3* can boost the survival and angiogenesis of PC-3 (a form of human PCa cell line). These results also indicated that *AKR1C3*-mediated tumor angiogenesis is regulated by androgen and estrogen metabolism. Subsequently, the potent combination of androgen and estrogen activates the insulin-like growth factor-1 (IGF-1) and AKT signal pathway followed by high vascular endothelial growth factor (VEGF) expression in PCa cells.[7]

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Breast cancer (BRC) patients who exhibit the overexpression of *AKR1C3* have a worse prognosis than those with lower expression levels. *AKR1C3* can increase the ratio of 17 β-estradiol to progesterone in breast tissue. Furthermore, the formation of PGF2α epimers has been shown to activate PGF receptors and deprive PPARγ of its putative anti-proliferative prostaglandin J2 (PGJ2) ligands.[8] In another study, Yoda *et al*.[1] reported that 11β-PGF2a, produced by the catalysis of *AKR1C3*, phosphorylates ERK and cAMP response element-binding protein (CREB) and then induces the overexpression of Slug in BRC cells *via* the PGF2α receptor. Therefore, *AKR1C3* reduces the sensitivity of BRC cells to chemotherapeutic drugs. These findings confirmed that the stimulation of 11 β-PGF2 α has a powerful effect on Slug related to EMT. Zhong *et al*[9] demonstrated that when *AKR1C3* was overexpressed, the tumor suppressor phosphatase and tensin homolog deleted on chromosome ten (*PTEN*) was lost, thus leading to a remarkable increase in activated AKT.

In endometrial cancer (EC), *AKR1C3* is considered one of the vital key enzymes of estrogen concentration. The actions of estrogen and progestin are regulated at the receptor level *via* the expression of estrogen and progesterone receptors, as well as at the pre-receptor level, by the interconversion of active hormones with their inactive counterparts. The expression of *AKR1C1* and *AKR1C3* in cases of EC determines the ratio of pregnendione (P) to estradiol (E2), thus influencing the progression of endometrial carcinoma.[10] Furthermore, Li and Narahara[11] demonstrated that a range of EC cell lines was all sensitive to the growth-inhibitory effect of 15-deoxy-Δ 12, 14-PGJ2, known to be the ligand for PPARγ. Besides, 15d-PGJ2 significantly up-regulated the expression of *AKR1C3* protein in three EC cell lines and that the cell cycle of EC was arrested in the G2 phase.

With regards to the relationship between *AKR1C3* and urinary bladder carcinoma (UBC), Figueroa *et al*[12] reported a strong association between the risk of UBC and variations in genes that were involved in the metabolism of polycyclic aromatic hydrocarbons (PAHs) and aromatic amines (AAs). These authors analyzed 65 SNPs in 15 candidate genes that are known to be activated by tobacco carcinogens and regulate the transcription of metabolic genes or code for products that can activate or detoxify PAH or AA. Results showed that genetic variation involved in genes that participate in the metabolism of carcinogens, especially *AKR1C3*, could be responsible for the high risk of

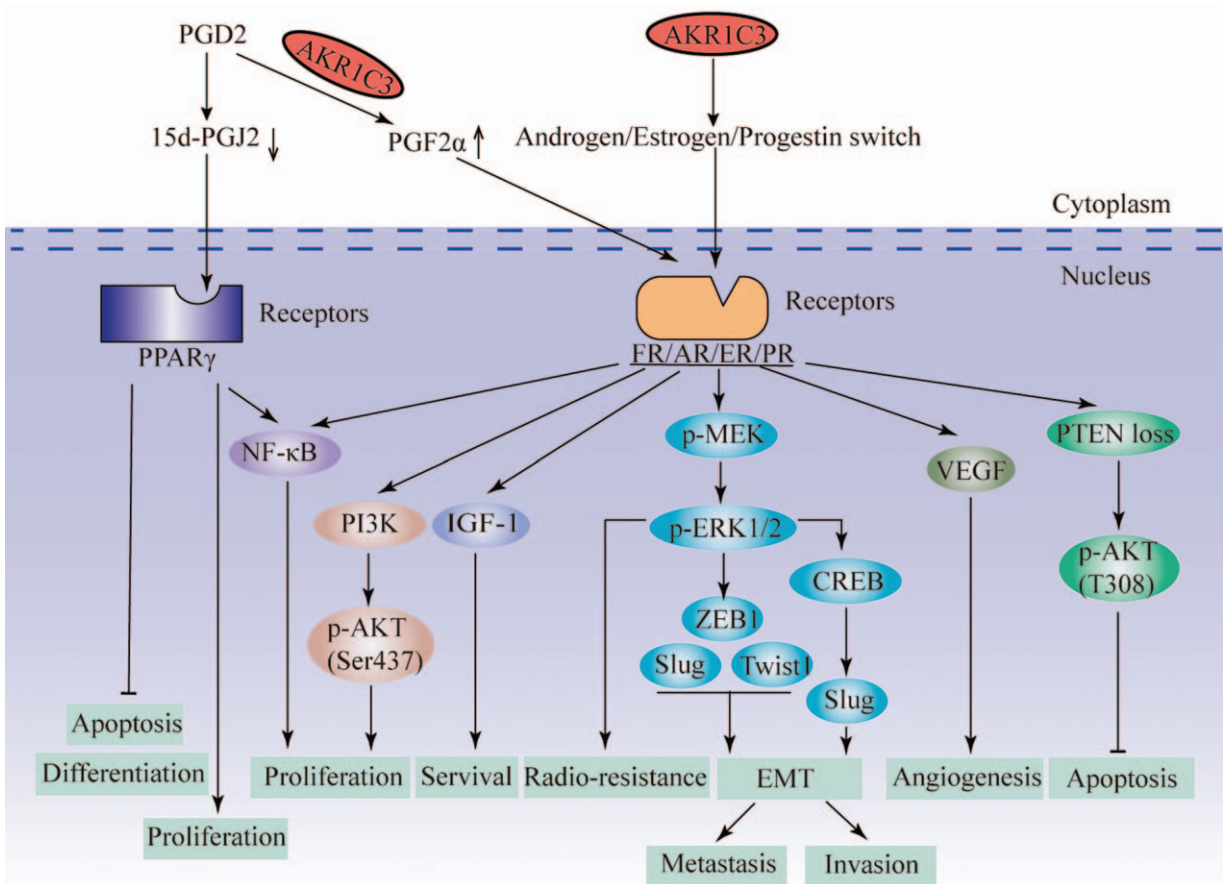

Figure 1: Overview of the major pathways for AKR1C3's action on tumor cells. *AKR1C3* promotes the proliferation, survival, radio-resistance, EMT, metastasis, invasion, and angiogenesis and inhibits the apoptosis, differentiation of tumor cells through the above signal pathway. 5d-PGJ2: 15-d prostaglandin J2; *AKR1C3*: C3 subtype of aldosterone reductase family 1; AKT: Protein kinase B; AR: Androgen receptor; CREB: cAMP-response element-binding protein; EMT: Epithelial-to-mesenchymal transition; ER: Estrogen receptor; FR: Prostaglandin receptor; IGF-1: Insulin-like growth factor-1; NF-κB: Nuclear factor kappa-B; p-AKT: Phosphorylated protein kinase B; PCD2: Prostaglandin D2; p-ERK1/2: Phosphorylated extracellular-regulated protein kinases 1/2; PGF2α: Prostaglandin F2α; PI3K: Phosphatidylinositol 3 kinase; p-MEK: Phosphorylated mitogen-activated protein kinase kinase; PPARγ: Peroxisome proliferator-activated receptor γ; PR: Progesterone receptor; PTEN: Phosphatase and tensin homolog deleted on chromosome ten; Twist1: Twist family BHLHT transcription factor 1; VEGF: Vascular endothelial growth factor; ZEB1: Zinc finger box-binding homeobox 1.

UBC. In a previous study, Tiryakioglu *et al*[13] reported a strong association between *AKR1C3* variants and the risk of UBC; the homozygous variant genotype of rs12529 was negatively correlated with UBC, while rs1937920 was positively correlated with an increased risk of UBC.

AKR1C3 plays an important role in regulating the proliferation, differentiation, and apoptosis of myeloid cells. Studies of acute myeloid leukemia (AML) have illustrated that the enforced overexpression of *AKR1C3* suppressed the ability of AML cells to differentiate when induced by all-trans retinoic acid (ATRA). In contrast, the down-regulation of *AKR1C3* in AML cells is known to mediate the differentiation. Studies by Verma *et al*[14] showed that a combination therapy, featuring an *AKR1C3* inhibitor, along with either etoposide or daunorubicin, elicited an effective adjuvant effect, in an AML cell line, thus potentiating the cytotoxicity of etoposide and daunorubicin by up to 6.25-fold and over 10-fold, respectively. More recently, Verma *et al* developed *AKR1C3* inhibitors by modifying a range of natural products. These inhibitors caused more than a 100-fold reduction in dose index, thus causing the complete re-sensitization of a daunorubicin-resistant AML cell line to a chemotherapeutic agent, and over a 100-fold dose reduction of the dose of cytarabine is not only AML cell lines but also primary T-acute lymphoblastic leukemia (T-ALL) cells.[15] However, at least in leukemia, the inhibition of *AKR1C3* alone is not enough to exert anti-leukemia effects. Because the leukemic properties of AML cells are consolidated by the combined activity of *AKR1C1–AKR1C4* [Supplementary Table 1, http://links.lww.com/CM9/A460 and Figure 1].

In summary, an increasing body of evidence supports the fact that *AKR1C3* plays a key role in malignancies. The up- or down-regulation of *AKR1C3* expression occurs in both hormone-dependent and hormone-independent tumors. The former type of tumor includes PCa, bladder cancer, BRC, and EC, while the latter form includes AML, gastric cancer, esophageal cancer, lung cancer, and brain tumors. The mechanism underlying how *AKR1C3* acts on malignant tumors is related to the diversity of this enzyme's characteristics; *AKR1C3* is known to play roles in a range of signal pathways, including the PI3K/Akt, MAPK, ERK, NF-κB, IGF-1/AKT, PTEN/AKT, and ERK/CREB signaling pathways. However, there are still many unanswered questions, especially in hormone-independent tumors. In future research, *AKR1C3* can be knockdown or overexpressed in cancer cells. And then investigate the potential influence of *AKR1C3* on the biological behavior of tumors, including migration, invasion, proliferation, differentiation, cell morphology, angiogenesis, and lymphatics. Such studies should involve immunohistochemistry, signaling pathways, bioinformatics analysis, omics, clinical research, and so on.

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Conflicts of interest

None.

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