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Orphan receptors in prostate cancer

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Running Title: Orphan receptors in prostate cancer.

Abstract: Background: The identification of new cellular receptors has been increasing rapidly. A receptor is called "orphan" if an endogenous ligand has not been identified yet. **Methods**: Here we review receptors that contribute to prostate cancer and are considered orphan or partially orphan. This means that the full spectrum of their endogenous ligands remains unknown. **Results**: The orphan receptors are divided into two major families. The first group includes G protein-coupled receptors. Most are orphan olfactory receptors. OR51E1 inhibits cell proliferation and induces senescence in prostate cancer. OR51E2 inhibits prostate cancer growth, but promotes invasiveness and metastasis. GPR158, GPR110 and GPCR-X play significant roles in prostate cancer development and progression. However, GPR160 induces cell cycle arrest and apoptosis. The other major subset of orphan receptors are nuclear receptors. RORα inhibits tumor growth, but RORγ stimulates androgen receptor signaling. PXR contributes to metabolic deactivation of androgens and inhibits cell proliferation. TLX has pro-tumorigenic effects in prostate cancer, while its knockdown triggers cellular senescence and growth arrest. Estrogen-related receptor ERRγ can inhibit tumor growth but ERRα is pro-tumorigenic. Dax1 and Shp are also inhibitory in prostate cancer. **Conclusion**: There is a "zoo" of relatively underappreciated orphan receptors that play key roles in prostate cancer.

Keywords: Orphan; receptors; nuclear; olfactory; prostate; cancer

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List of abbreviations

GPCR: G protein-coupled receptor
cAMP: Cyclic adenosine monophosphate
FDA: Food and Drug Administration
LBD: Ligand-binding domain
DBD: DNA-binding domain
DNA: Deoxyribonucleic acid
FXR: Farnesoid X receptor
LXR: Liver X receptor
ROR: Retinoic acid-related orphan receptor
PXR: Pregnane X receptor
TLX: Homologue of the Drosophila tailless
Dax1: Dosage sensitive sex reversal (DSS), adrenal hypoplasia congenita (AHC) critical region on the X chromosome, gene 1
Shp: Small heterodimer partner
AR: Androgen receptor
OR: Olfactory receptor

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MAPK: Mitogen-activated protein kinase
AKT: Protein kinase B
Rho: Rhodopsin
OR4A47: Olfactory receptor family 4 subfamily A member 47
GNAO1: G protein subunit alpha O1
GNA13: G protein subunit alpha 13
GNAI1: G protein subunit alpha I1
LNCaP: Lymph node carcinoma of the prostate (cell line)
PI3K: Phosphoinositide 3-kinase
NF-KB: Nuclear factor-kappa B
ERK1/2: Extracellular-signal-regulated kinase 1/2
TAS2R: Taste 2 receptor
MEK: Mitogen-activated protein kinase kinase
p38MAPK: p38 mitogen-activated protein kinase
PARP: Poly(ADP-ribose) polymerase 1
PIN: Prostatic intraepithelial neoplasia
TRAMP: Transgenic adenocarcinoma of the mouse prostate
ABCB1: ATP binding cassette subfamily B member 1
GPR158: G protein-coupled receptor 158
PTEN: Phosphatase and tensin homolog
PC3: Prostate cancer cell line
DU145: Prostate cancer cell line
RORE: ROR response elements
SRC: SRC proto-oncogene, non-receptor tyrosine kinase
ACTR: Acid tolerance regulatory protein
SULT2A1: Sulfotransferase family 2A member 1
CYP3A: Cytochrome p450 family 3 subfamily A
GFAP: Glial fibrillary acidic protein
Pax2: Paired box 2
H-Ras: Harvey rat sarcoma virus (oncogene)
CDKN1A: Cyclin dependent kinase inhibitor 1A
SIRT1: Sirtuin 1
HDAC1: Histone deacetylase
ERR: Estrogen related receptor
PGC1: Peroxisome proliferator-activated receptor gamma coactivator 1
ARE: Androgen response element
AKR1C3: Aldo-keto reductase family 1 member C3
AMPK: AMP-activated protein kinase
ER: Estrogen receptor
SRY: Sex-determining region Y
MiR-141: micro-RNA 141

Introduction

It has been recently discovered that steroid, retinoid and thyroid receptors constitute only a small fraction of a group of similar gene products. The identification of new classes of receptors with similar structures to existing ones, has been increasing at a rapid pace[1]. A receptor is called "orphan" if an endogenous ligand has not been identified yet[2]. If a ligand is later discovered, the receptor is referred to as "adopted orphan". This is the key to understanding their physiological role. Extensive research on these newly discovered receptors suggests that there are several cellular signaling pathways that remain to be discovered[2].

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The orphan receptors are divided into two major structurally distinct families[3,4]. The first group includes the G protein-coupled receptors (GPCRs)[3]. They form a large group of evolutionarily-related proteins[5,6]. There are nearly 100 receptor-like genes that remain orphans in the GPCR family[6,7]. They are cell membrane receptors that interact with extracellular molecules to activate cellular responses. GPCRs pass through the outer membrane seven times and are coupled with G-proteins[7]. They are found only in eukaryotes and animals and they are activated by ligands such as neurotransmitters, odors, pheromones and hormones[7,8,9]. The signal transduction pathways that originate from GPCRs include either the phosphatidylinositol signal pathway or the cAMP signal pathway[7,9]. Their signaling pathways are involved in several diseases and currently about 34% of the FDA approved drugs target them[10]. There are five main phylogenetic families of GPCRs: glutamate, rhodopsin, adhesion, frizzled/taste2 and secretin. Approximately 49% of GPCRs in humans are olfactory receptors. Despite the deorphanization efforts, most olfactory receptors still remain orphans[7]. Many taste receptors remain orphans as well[11].

The other major subset of orphan receptors is the family of nuclear receptors[1]. They are cytosolic proteins. After ligand-binding activation, they change their spatial conformation and translocate to nuclear binding sites to act as transcription factors. They modulate gene expression in response to a wide range of physiological, developmental and environmental cues. Some nuclear receptors also mediate non-genomic effects that are too rapid to involve gene transcription changes. The nuclear receptors are usually composed of 4 different functional modules. These are the ligand-binding domain (LBD), the DNA-binding domain (DBD), the hinge region, and the modulator domain[1]. Examples of orphan nuclear receptors include the Farnesoid X receptor (FXR), the Liver-X receptor (LXR), the Retinoic acid receptor-related orphan receptors (RORs), the Pregnane X receptor (PXR), the TLX receptor, the Estrogen-related receptors, the Dax1 receptor, the Shp receptor, and others[1,12,13]. However, the endogenous ligands for FXR and LXR have been identified as bile acids and endogenous oxysterols respectively[14,15]. Hence, these receptors are considered adopted (i.e., de-orphanized).

Prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer-related death in American men[16]. The activation of androgen receptor (AR) signaling axis is of paramount importance, not only during the androgen sensitive stage, but also during the castration resistant stage[17]. However, it has been increasingly evident that other receptors also play important roles in prostate cancer development and progression, alone or in coordination with AR[18]. Examples not only include other steroid nuclear receptors such as the glucocorticoid and progesterone receptor, but also retinoic acid and retinoid X receptors, the hepatocyte nuclear factor, the peroxisome proliferator-activated receptors, the liver X receptors, and others[18]. Several G protein-coupled receptors and receptor tyrosine kinases are also of paramount importance[19,20]. Here we will review a few classes of receptors that contribute to prostate cancer tumorigenesis and progression, that are considered orphan or partially orphan. This means that the full spectrum of their endogenous ligands has not been discovered yet.

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Olfactory receptors

Olfaction is a form of chemosensation and is the most ancient human sense[21]. Modern human olfactory receptors have evolved from ancient chemosensors that existed on the surface of primitive cells[21,22]. Odor molecules are detected by olfactory receptors that are predominantly located on the main olfactory epithelium in the nasal cavity. OR genes are the largest multigene family in the vertebrates, since there are thousands of different odors that need to be distinguished[21,22]. OR genes in the human genome account for approximately 400 functional genes and numerous pseudogenes[22,23]. ORs are G-protein-coupled receptors and they have seven transmembrane alpha-helical regions[22]. They belong to the superfamily of rhodopsin-like GPCRs and apart from odorants, other ligands include neurotransmitters, chemokines, peptides, lipids and nucleotides[22,24]. Only a small fraction of the activating odorants has been identified[25]. Once ORs recognize odorant molecules, they activate a signal transduction pathway that leads to the perception of smell[26,27]. This process also regulates the apoptotic cycle of olfactory sensory neurons[28]. In addition, they activate pathways associated with proliferation, such as MAPK, AKT and Rho[28]. Some ORs also play a role in migration, as they mediate the projection of olfactory sensory neurons towards specific structures in the olfactory bulb[28,29]. However, ORs are also expressed in other non-nasal tissues and they likely have pleiotropic effects. For example, skin regeneration and hair growth can be regulated by ORs[30,31].

Cancer cells in general express low levels of OR genes, but around 20 percent of tumors overexpress one or a few receptor genes. Around 70% of the cells that express at least one OR, overexpress only one specific receptor[28]. Frequently, ORs overexpressed in cancer cells are normally silent in normal cells, suggesting that there is a different transcription repertoire in cancer[32]. Commonly overexpressed ORs in tumor cells include OR4A47, OR4C46, OR6B2 and OR1D5[28]. In addition, tumor cells that overexpress an OR also express the necessary functional effectors for signal transduction. Examples include the alpha subunits of a G-protein: GNAO1, GNA13, GNA15, GNAI1, GNAL and adenylate cyclase 3[28]. Overall, this suggests that the aberrant expression of ORs might contribute to the cancer phenotype. In cancer cells, ORs act as chemoreceptors[33]. In comparison to healthy prostate tissue, prostate cancer shows a high tumor-specific overexpression (i.e., more than 10-fold) of OR51E1 and OR51E2 in two-third of cases[34]. The full spectrum of their ligands is still unknown, but deorphanization efforts showed that they can be activated by lactate, butyric acid, propionic acid, and other aliphatic acids[34]. The activation of OR51E2 by the ligand beta-ionone leads to inhibition of prostate cancer cell proliferation, by blocking the androgen receptor nuclear translocation[35]. However, beta-ionone stimulation of OR51E2 in LNCaP cells promotes a PI3K-gamma-dependent increase in tumor invasiveness and metastatic potential[36]. The effects of beta-ionone are also likely mediated by MAPK activation and intracellular calcium ion increase[37]. In addition, changes in OR51E2 expression have been associated with activation of NF-kB and protein kinases[34]. OR51E2 is expressed in normal prostate epithelial tissue, which suggests that it might play a physiological role[38]. Moreover, experiments have shown that the activation of OR51E1 inhibits cell proliferation and

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induces senescence in prostate cancer[34]. Upregulation of OR51E1 promotes cell death by increasing phosphorylation of ERK1/2 and upregulating p53[34]. Olfactory receptors are also likely activated by steroid hormones, such as androstenone and androstadienone[37]. This suggests that androgen pheromones may initiate rapid non-genomic actions through OR activation[37]. In humans and other animals, pheromones are not only regulators of behaviour, but they affect neurogenesis and pose neuroendocrine effects as well (e.g., hypothalamus-pituitary-gonadal axis)[39,40]. Recent evidence suggests that 19-Hydroxyandrostenedione induces neuroendocrine transdifferentiation in prostate cancer cells via OR51E2[41].

Taste receptors

It has been shown that gustatory receptors also play a role in prostate cancer[42]. Taste has evolved in animals to provide gratification from food[43]. Similar to olfaction, gustation is behavior-modifying[43,44]. Bitter taste perception is critical for survival because it enables an organism to avoid the ingestion of potentially harmful substances[44]. Salty and sour compounds are linked to ion channels, while bitter, sweet and umami flavours are connected to G-protein-associated receptors[45]. Bitter taste receptors (TAS2Rs) have been identified in non-gustatory organs and have been linked to various diseases, including cancer[46]. In several tumor types, TAS2R activation exerts various anti-cancer effects, such as increased apoptosis and decreased cell proliferation and migration[46,47,48]. The expression levels of most TAS2Rs are diminished in prostate cancer cell lines compared to benign prostatic hyperplasia[47]. Recent studies suggest that noscapine causes a TAS2R14-dependent cell death induction and decreased viability in prostate cancer cells[47]. Bitter melon extract (BME) also selectively kills cancer cells (>90%) and spares normal prostate epithelial cells[49]. Prostate cancer cells treated with bitter melon extract (BME) tend to accumulate in S-phase. BME strongly modulates cyclins, inhibits normal cell-cycle regulation, activates MEK-ERK or p38MAPK signaling pathways, enhances Bax expression and induces PARP cleavage[49]. It also induces apoptosis in prostate cancer cells and delays the progression of PIN in TRAMP mice[49]. In general, most TAS2Rs exert anticancer effects. A notable exception is TAS2R38, which is frequently overexpressed in cancer compared to normal tissue[46]. TAS2R38 can upregulate multidrug resistance protein ABCB1 and can induce chemoresistance in several tumor types[46].

Other orphan G protein-coupled receptors

The G protein-coupled receptor 158 (GPR158) is an orphan receptor, which is a member of the glutamate family of GPCRs[50]. It plays a significant role in prostate cancer development and progression. It promotes tumor cell proliferation independently of AR, and this requires its localization inside the nucleus[50]. Moreover, GPR158 stimulates AR expression, while androgens stimulate GPR158 expression . This implies a potential role of the receptor in tumor sensitization to low androgen levels during androgen deprivation therapy. GPR158 is also associated with the development of neuroendocrine phenotype and promotes anchorage-independent tumor cell colony formation[50]. Increased expression is associated with lower disease-free survival. In a genetically

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defined conditional PTEN knockout mouse model, the expression of GPR158 was increased at the invading front of prostate cancer[50]. GPCR-X is another orphan G protein-coupled receptor that is associated with cellular transformation and tumor growth in prostate cancer. Inactivation of this receptor in PC3 cells resulted in 80-100% tumor regression rates in an athymic xenograft tumor model[51]. Moreover, seventeen percent of the mice became disease free. The effects of GPCR-X are mediated by downregulation of the cell adhesion pathway[51]. GPR110 is an orphan GPCR that is highly expressed in prostate cancer[52]. Lum et al. showed that staining with GPR110 antibody during immunohistochemistry, was able to differentiate between potential incipient malignancy and benign prostatic hyperplasia[52]. On the contrary, GPR160 is an orphan GPCR that has been associated with cell cycle arrest and induction of apoptosis in prostate cancer cells[53].

Retinoic acid receptor-related orphan receptors

Retinoic acid receptor-related orphan receptors (RORs) are nuclear receptors that include RORα, RORβ and RORγ[54]. They activate transcription through ligand-dependent interactions with co-regulators[54]. They play important roles in brain and retinal development and drive naive T-cell lineage specification towards Th17 cells[54,55]. They are also involved in circadian rhythm regulation and metabolic homeostasis[54]. Several cholesterol derivatives and retinoids have been shown to regulate ROR activity[54]. Studies have found that RORα and RORβ act as tumor suppressors in several cancer types. On the contrary, RORγ plays diverse roles in distinct cancers[54]. Park et al. found decreased expression of RORα in prostate cancer[56]. It has been shown that RORα can inhibit cell proliferation in LNCaP cells, via the downregulation of Wnt target genes[56]. It can also induce growth arrest in DU145 cells, both in vitro and in vivo[57]. Moreover, RORα can control the metastatic behavior in subsets of androgen-independent tumors[58]. RORγ on the other hand, has been established as an important oncogenic driver in prostate cancer[59]. Although RORγ is overexpressed in about 50% of prostate adenocarcinoma, it is particularly amplified in metastatic castration-resistant disease. RORγ protein is not detected in normal prostate epithelial cells[59]. It binds to an exonic RORE and directly stimulates androgen receptor gene transcription. The AR locus contains several putative ROREs. Furthermore, RORγ recruits the co-factors SRC-1 and SRC-3/ACTR, that occupy the AR-RORE site[59].

Pregnane X receptor

The Pregnane X receptor (PXR) is a nuclear receptor that regulates genes encoding transporters and enzymes responsible for the metabolism and elimination of endogenous compounds and xenobiotics. It is remarkably promiscuous and shows a broad ligand specificity[60,61]. It plays a key role in the metabolism and eventual elimination of steroids, bile salts and environmental contaminants across species[60]. PXR is expressed in prostate cancer but its expression levels in localized disease decreases in Gleason scores above 6[61,62]. High PXR expression in radical prostatectomy specimens is associated with better prognosis and increased survival[62]. PXR induces the expression of hydroxysteroid sulfotransferase (SULT)2A1 and several members of cytochrome p450

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CYP3A enzymes, which contribute to the metabolic deactivation of androgens[63]. In human prostate cancer, PXR partially inhibits androgen-dependent cell proliferation, but has no effect in androgen-independent proliferation[63]. Interestingly, despite the antiandrogenic effects, it does not cause reproductive defects in a normal individual, perhaps due to hypothalamus-pituitary testis axis compensation[63]. Recent evidence suggests that PXR also acts as a negative regulator of apoptosis, via downregulation of p53[64]. Hence, it can promote a malignant phenotype. In addition, it plays a major role in the detoxification of chemotherapeutics[61]. Pre-activation of PXR leads to increased resistance to chemotherapy in prostate cancer cells[61,62]. The downregulation of PXR re-sensitizes these cells to chemotherapy. Moreover, the expression of PXR increases in the castration resistant setting[62]. This suggests that PXR in later stages plays a role in the metabolic clearance of therapeutic compounds and the development of a treatment-resistant phenotype.

TLX receptor

TLX is an evolutionary conserved nuclear receptor that plays a critical role in embryonic and adult neurogenesis[65,66]. It is usually found in proliferating neural progenitors, regulating adult neural stem cell renewal[65,66,67]. It has been suggested that retinoids can act as ligands[65]. Aberrations in the TLX gene leads to loss of neurogenesis, retinopathies, psychiatric conditions and nervous system tumors. TLX expression in neural stem cells is crucial for maintaining their undifferentiated state[65,66,67]. The expression of TLX decreases as the neural progenitor cells differentiate[67]. Target genes include PTEN, GFAP, p21 and Pax2[65,67]. TLX can suppress oncogene induced senescence, thus contributing to the proliferating phenotype and also promoting tumorigenesis[68]. TLX is the most frequently altered orphan nuclear receptor in prostate cancer[61]. Its expression levels are increased in high Gleason score disease and several prostate cancer cell lines[69]. It was shown that TLX overexpression has pro-tumorigenic effects in prostate cancer, while its knockdown triggers cellular senescence and growth arrest in vitro and in vivo[69]. Upregulation of TLX prevents prostate epithelial neoplasia cells from undergoing senescence during PTEN knockdown or oncogene H-Ras activation, via CDKN1A repression and SIRT1 transactivation[69]. It can also repress p21, which is a prominent senescence-related gene[68]. In addition, TLX can confer resistance to androgen deprivation and anti-androgens[70]. Interestingly, it can directly suppress AR gene transcription and signaling in prostate cancer cells that are already castration resistant, regardless of the androgen stimulation status[70]. TLX can bind directly to the AR promoter and repress the transcription of AR, via recruitment of histone modifiers, such as LSD1, HDAC1 and HDAC3. At the same time, it increases the expression of neuroendocrine markers[70].

Estrogen-related receptors

It has been suggested that the first ancestral steroid receptor was closer to the estrogen receptor (ER)[71]. Although steroid receptors are not found outside vertebrates, an ortholog of the estrogen-related receptor (ERR) is present in the genome of Drosophila melanogaster[71]. ERRs have three subtypes, ERRα, ERRβ and ERRγ[72,73]. They are constitutively active

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without the presence of estrogens[73]. However, they bind to the same response elements as the ER and there is a crosstalk and overlap between their downstream signaling pathways[61]. The ERR family interacts with the transcriptional co-regulators PGC1-alpha and PGC1-beta and plays a central role in mitochondrial biogenesis and the regulation of cellular energy metabolism[72,73]. ERRs respond to changes in nutrients and energy demands, to regulate multiple metabolic activities and orchestrate growth and differentiation[72,73]. Although the expression of ERRβ in normal prostate tissue is high, it is lost in cancer[61,74]. On the other hand, ERRα and ERRγ are consistently expressed in prostate cancer[61,75]. High ERRα expression is a poor prognostic factor[75]. ERRα protects against hypoxia and enhances tumor cell proliferation and invasiveness in prostate cancer[76,77,78]. It also binds to androgen response elements (AREs) and drives AR gene transcription and signaling, independently from AR[79]. ERRα also contributes to castration resistance via direct transactivation of the androgen synthesis enzymes AKR1C3 and CYP11A1[80]. In addition, it can modulate prostate cancer cell metabolism, by regulating metabolic pathways downstream from the master regulator AMP[81]. The expression of ERRγ is slightly lower in prostate cancer compared to normal prostate tissue. It has been shown that ERRγ can inhibit tumor growth and reduce cellular proliferation in prostate cancer cell lines, by inducing p21 and p27[61,82].

Dax1 and Shp

Dax1 is a nuclear receptor that lacks a DNA-binding domain[61,83]. It binds to other chromatin-bound nuclear receptors, such as AR and ER, and inhibits their action[84,85]. The interaction between Dax1 and the nuclear receptors blocks the binding of coactivators, and encourages the recruitment of corepressors[61,86]. It also inhibits the dimerization of AR[61,87]. During embryonic development, Dax1 plays an important role in the normal development of hormone producing tissues[88]. In addition, it regulates the production of steroid hormones in these tissues[89]. It acts antagonistically to the SRY gene and Dax1 locus duplication is associated with male-to-female reversal[90]. Mutations in the Dax1 gene cause hypogonadotropic hypogonadism and X-linked congenital adrenal hyperplasia[91,92]. Dax1 was shown to repress AR activity in LNCaP cells[86,93]. Its expression in prostate cancer is inversely correlated with Gleason score[94]. Dax1 inhibition with oncomiR miR-181 promotes prostate cancer cell proliferation[93]. The short heterodimeric partner (Shp) is a similar orphan nuclear receptor that lacks a DNA-binding domain[61,95]. It also affects the transcriptional activity of chromatin-bound nuclear receptors by interfering with the coregulator interactions[61,95]. Moreover, Shp intercepts with the DNA binding of nuclear receptors[96]. Overall, it interacts with several other nuclear receptors, including the androgen receptor[95,97]. Shp acts as a mediating factor in the metabolic circadian clock[98]. It has been shown that some atypical retinoids can act as ligands to promote its activity[99]. MiR-141 results in translational suppression of Shp, while phenethyl isothiocyanate (which is found in many edible cruciferous vegetables) increases its expression[100]. Shp is downregulated in multiple prostate cancer cell lines[100]. Its overexpression attenuates AR signaling in LNCaP cells[100,101]. Shp was also shown to induce apoptosis in DU-145 prostate cancer cells[102].

Conclusions

There is a "zoo" of receptors that play key roles in prostate cancer. The significance of the orphan receptors has been relatively underappreciated, but recent findings highlight their importance in the development and progression of prostate cancer. Several orphan receptors can be activated by endogenous compounds. Most have a wide specificity for ligands. Some have pro- and others have anti-tumorigenic activity. This underscores the complexity of molecular signaling inside the cancer cells. Experimental evidence has shown that targeting the activity of these orphan receptors can have a significant impact in the progression of the disease. This raises the possibility that future scientific and technological advances might enable every patient's tumor to be analyzed not only for genetic aberrations, but also for receptor expression status. Aberrations in orphan receptors might provide additional therapeutic targets that can be targeted with limited toxicity.

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