5

Steroid Receptors in Renal Cell Carcinoma

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1. Introduction

Renal cell carcinomas (RCCs) are the most common epithelial neoplasms of adult kidney. It has been estimated that there will be about 60,920 new cases of kidney cancer in the United States in 2011 and about 13,120 people will die from this disease (Siegel et al. 2011). Currently, surgery remains the only effective treatment for RCC, since metastatic disease is highly resistant to radiotherapy and chemotherapy. Approximately 20 to 30% of patients with RCCs present with non-resectable metastatic disease and 20 to 40% of patients undergoing nephrectomy for clinically localized RCC will develop metastatic disease. In the past two decades significant advances in the diagnosis and treatment of patients with RCC have resulted in improved survival of a select group of patients. Prior to the availability of targeted therapies, Interferon-α (IFN) was the standard of care but was associated with a low response rate and significant toxicity (Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomized controlled trial. Medical Research Council Renal Cancer Collaborators 1999). High dose interleukin-2 (IL-2) has a similar response rate as IFN, but can cure approximately 3-5% of patients (Yang, Sherry, et al. 2003). Targeted molecular therapies include inhibitors of angiogenesis (Yang, Haworth, et al. 2003), inhibitors of receptor tyrosine kinases with promiscuous targets including VEGFR1 and VEGFR2, PDGFR, C-Kit, Raf kinase, mammalian target of rapamycin (mTOR) (Atkins et al. 2004; Motzer et al. 2006; Porta et al. 2011) and combination treatment modalities (Escudier et al. 2007; Hudes et al. 2007; Motzer et al. 2007). These novel therapies have demonstrated improved outcomes and have become the first line of therapy in patients with advanced metastatic disease or second line of therapy in patients who have failed prior cytokine immunotherapy (Leveridge & Jewett 2011). As new treatment modalities become standard of care, clinical practices in diagnosis and treatment of the primary tumor will undergo revision. For instance, the role of cytoreductive surgery in patients selected for targeted therapy has not yet been established. This could increase the number of cases diagnosed and treated based on core needle biopsies alone, presenting new challenges to surgical pathologists who will likely have to use smaller amounts of tissue to accurately classify the tumor and provide molecular information aimed to personalize clinical care.

RCC is a heterogeneous neoplasm, which includes distinct histological subtypes (Table 1). Among the adult population, clear cell RCC constitutes the most prevalent subtype (70-80%)

Histological Subtype	Incidence	5-Year Survival	Cell of Origin
Clear Cell RCC	70-80%	45-76%	Proximal convoluted tubules
Papillary RCC	10-15%	82-90%	Shared phenotype of proximal and distal tubules
Chromophobe RCC	5%	78-92%	Intercalated cells of collecting tubules and ducts
Oncocytoma	5%	100%	Intercalated cells of collecting tubules and ducts

Table 1. Major Histological Subtypes of Renal Cell Neoplasms with Corresponding Incidence, Survival, and Cell of Origin

and has a relatively unfavorable prognosis (Amin et al. 2002; Eble et al. 2004). Papillary and chromophobe RCCs are less common, comprising 10-15% and 5%, respectively, and have a better prognosis compared to clear cell RCC (Amin et al. 2002). Oncocytoma is a benign renal cell tumor characterized by an extremely favorable prognosis. Renal epithelial tumors are thought to originate in cells of different compartments along the nephron. Clear cell RCC is believed to arise from the proximal tubules. Tumors that originate in the collecting tubules and ducts include chromophobe RCC, oncocytomas, and the more rare collecting duct and medullary carcinomas. The histogenesis of papillary carcinoma is controversial with some studies suggesting a proximal tubule origin while phenotyping by immunohistochemistry supports a distal nephron origin. Renal tumors with papillary growth include papillary RCC types 1 and 2, clear cell RCC with papillary features and the recently described clear cell papillary RCC (CPRCC) (Gobbo et al. 2008). CPRCC is a subtype of renal cell carcinoma characterized by cells with clear cytoplasm arranged in papillary structures which was first described in patients with end stage renal disease, but later also identified in kidneys unaffected by end stage renal disease (Fuzesi et al. 1999; Gobbo et al. 2008).

Immunohistochemistry is useful in distinguishing the different subtypes of renal neoplasms. Clear cell RCCs are frequently CD10 positive but AMACR and CK7 negative; papillary carcinoma, on the other hand, is positive for CK7 and AMACR and usually negative for CD10. Recent studies in CPRCC demonstrate positive immunoreactivity for CK7 but negative AMACR and CD10. These and other immunohistochemical markers are currently used routinely in diagnostic histopathology to help classify tumors. However, this is a constantly evolving field and new immunohistochemical and molecular markers are being investigated to address new clinical needs.

Steroid receptors are a family of ligand dependent transcription factors, which have important roles in control of growth and differentiation in many non-neoplastic and neoplastic cell types. The steroid receptor family is characterized by a unique modular structure, with receptors classically divided into three main domains and several

Steroid Receptor	Expression in Normal Kidney	Tumor Type	Clinical Relevance	References
GR	Proximal tubules, glomeruli	Clear cell RCC	Increased expression is a favorable marker	Yakirevich et al. 2011
MR	Distal tubules, loops of Henle and collecting ducts	Oncocytoma and chromophobe RCC	Diagnostic marker	Yakirevich et al. 2008
ER	Interstitial stromal cells	Cystic nephroma, mixed epithelial and stromal tumor, angiomyolipoma with epithelial cysts	Hormonal mechanism of pathogenesis	Adsay et al. 2000
PR	Interstitial stromal cells	Cystic nephroma, mixed epithelial and stromal tumor, angiomyolipoma with epithelial cysts, chromophobe RCC and oncocytoma	Hormonal mechanism of pathogenesis Diagnostic marker	Adsay et al. 2000 Tickoo et al. 2008 Mai et al. 2008
AR	Proximal and distal tubules	Clear cell, papillary, and chromophobe RCC	Increased expression is a favorable marker	Kimura et al 1993 Langner et al, 2004
VDR	Distal tubules and collecting ducts	Papillary RCC, chromophobe RCC, oncocytoma, collecting duct carcinoma	Diagnostic marker	Obara, Konda et al. 2007 Liu et al. 2006
RAR and RXR	Proximal tubules, interstitial cells	Clear cell RCC, chromophobe RCC (RAR-β)	Increased expression of RXR-γ is a favorable marker	Goelden et al. 2005 Obara, Konda et al. 2007

Table 2. Steroid Receptors in Renal Cell Neoplasms

subdomains or regions. In general, the receptor members share a variable amino-terminal transactivation domain, a central and well-conserved DNA-binding domain (DBD), and a moderately conserved carboxy-terminal domain responsible for ligand binding. The latter domain also contains activating functions. The well known members of the steroid receptor family includes glucocorticoid (GR), mineralocorticoid (MR), progesterone (PR), androgen (AR), estrogen (ER), vitamin D (VDR), thyroid, and retinoic acid (RAR)/retinoid X receptors (RXR) (Fuller 1991).

There is emerging evidence that steroid receptors can induce gene expression through both ligand-dependent and ligand-independent pathways, and distinct families of genes are likely to be regulated depending on the mechanism of nuclear receptor signaling. Until recently, the study of steroid receptors in renal cell neoplasm's (RCNs) has been limited to ER and PR. The employment of novel techniques for studying steroid receptors in RCCs, such as immunohistochemistry, tissue microarray technology, and quantitative real-time PCR has revealed the presence and biologic importance of several steroid receptors in RCNs, including GR, MR, VDR, and others (Table 2). This review will focus on histogenetic, diagnostic, and prognostic implications of steroid receptor expression in RCNs.

2. Glucocorticoid receptor

Glucocorticoids mediate their effects via their intracellular glucocorticoid receptors. Studies of GRs have revealed that there is only one GR gene, but several GR receptor isoforms resulting from alternative splicing or alternative translation initiation (Pujols et al. 2002; Revollo & Cidlowski 2009). Two main human isoforms, GR-α and GR-β, have a different distribution pattern and biologic activity in healthy and diseased human cells and tissues. It has been demonstrated that GR-α is the predominant isoform expressed in a large number of healthy human tissues including brain, liver, kidney, skeletal muscle, lung, and other organs. The GR- α isoform possesses steroid binding activity. In contrast, GR-β expression level is lower than that of the GR- α isoform and is relatively abundant in inflammatory blood cells (Pujols et al. 2002). In non-activated cells, the GR resides in the cytoplasm as a part of a large complex consisting of chaperone and cochaperone proteins including heat shock proteins hsp90, hsp70, immunophilins FKBP51 and FKBP52, and others (De Bosscher et al. 2003). Upon ligand binding, GR undergoes phosphorylation and activation and translocates from the cytoplasm to the nucleus where it converts to a DNA-binding form. Transcriptional responses triggered by activated GR include both positive and negative gene regulation. The direct positive transcriptional regulation of genes (transactivation) requires binding of the GR homodimer to glucocorticoid-response elements (GRE) in gene promoters. The indirect negative regulation (transrepression) is mediated through negative cross-talk with other transcription factors including AP-1, NF-kB and p53 (Beato et al. 1995). As a result, glucocorticoids modulate a variety of physiologic and pathologic processes, including among others cellular differentiation, growth, inflammation, immune response, and carbohydrate metabolism.

2.1 Expression of GR in the normal kidney

In normal human kidneys GRs contribute to the regulation of renal fluid and electrolyte homeostasis. Keeping with their physiologic function, GRs are differentially distributed

along the kidney nephron. *In vitro* studies have implicated GRs in the regulation of ammoniagenesis, gluconeogenesis, GFR, Na-H exchange and Na-phosphate co-transport, all of which are proximal renal tubule processes (Baylis et al. 1990; Boross et al. 1986; Campen et al. 1983; Freiberg et al. 1982). Measurement of GRs in normal rat kidney cortical tubules enriched in proximal tubules yielded three to six fold higher GR content as compared to the distal tubules (Mishina et al. 1981). Predominant proximal tubule localization of GR was demonstrated by quantitation of GR mRNA levels in microdissected nephron segments from the rat kidney by a competitive polymerase chain reaction (PCR) technique (Todd-Turla et al. 1993). GR mRNA was twofold more abundant in glomeruli, proximal tubule, and thick ascending limb segments than in the collecting duct segments (Todd-Turla et al. 1993). In an additional study GR mRNA was localized by in-situ hybridization predominantly to renal proximal tubules and cortical collecting tubules with lower levels in distal collecting tubules of the rat kidney (Roland et al. 1995). In a recent study we provided immunohistochemical evidence of GR expression in the proximal tubular epithelium of normal human kidneys and in the epithelial cells of normal renal glomeruli (Yakirevich et al. 2011). However, several *in vitro* and *in vivo* studies have demonstrated that glucocorticoids can exert mineralocorticoid-like effects, such as Na+ reabsorption and K+ secretion, in the distal nephron (Morris & Souness 1992; Naray-Fejes-Toth & Fejes-Toth 1990; Thomas et al. 2006).

2.2 Expression of GR in kidney tumors

Initial studies of GR expression in RCCs based on ligand-binding assays in the early 1980's demonstrated the presence of GRs in kidney tumors (Bojar et al. 1979; Chen et al. 1980; Hemstreet et al. 1980; Liu et al. 1980). In these pioneer studies renal tumors were not subdivided into different histologic subtypes and were all designated as RCCs. Bojar et al. demonstrated GRs in 10 of 15 tumors studied (Bojar et al. 1979). The average dexamethasone binding capacity was calculated and found to be 7.1 fmol/mg of cytosol protein. The ligand specificity experiments clearly indicated that binding to GRs is not restricted to glucocorticoids alone. Progesterone and aldosterone turned out to be moderate competitors for dexamethasone binding. Medroxyprogesterone acetate, the compound widely used in hormone therapy of advanced renal cancer in man, was demonstrated to be one of the strongest inhibitors of [3H] dexamethasone. The binding of medroxyprogesterone acetate to GRs may represent the primary mechanism of action of the compound in causing tumor regression. Hemstreet et al. identified and measured the levels of GRs in 47 autologous pairs of normal and neoplastic renal tissue (Hemstreet et al. 1980). Glucocorticoid receptors were demonstrated in this study in normal and neoplastic tissues of both sexes. The levels of GRs were higher in the tumors (mean 31.3 fmol/mg) than in the normal tissue (18.5 fmol/mg). In an additional study conducted at the same time, Liu et al. reported high concentrations of GRs in four of seven RCC cases (Liu et al. 1980). The levels of GRs in RCCs were comparable to those in the glucocorticoid-responsive rat liver. Furthermore, the GR levels in RCCs were comparable to human acute lymphocytic leukemia cells sensitive (0.03 pmol/mg cytosol protein), in contrast to those that have become resistant (0.015 pmol/mg cytosol protein) to glucocorticoids. Chen et al. detected GRs in cytosol of RCCs (Chen et al. 1980). Competition experiments demonstrated that progestin competed for the GR sites in all renal tumors tested, whereas diethylstilbestrol and testosterone were weak or not competitive.

Development of antibodies against human GR enabled immunohistochemical and Western blot assessment of GR protein expression. In addition, molecular studies utilizing reverse transcriptase polymerase chain reaction (RT-PCR) revealed that most commonly used RCC cell lines express high levels of GR. In a study by Arai et al., two RCC cell lines OUR-10 and NC65 expressed high levels of GR, whereas Caki-1 cell exhibited low levels of GR expression by Western blot (Arai et al. 2008). Iwai et al. demonstrated GR mRNA expression in the A498, RCC270, Caki1, and ACHN renal carcinoma cells. A498 and RCC270 expressed especially high levels of the GR gene (Iwai et al. 2004). Recently, using tissue microarray technology and real-time RT-PCR we described the immunohistochemical and mRNA expression of GRs in different histologic subtypes of RCNs including clear cell RCC, papillary RCC, chromophobe RCC, and oncocytoma (Yakirevich et al. 2011). We found that GRs are strongly expressed in the majority of clear cell RCCs (66%), in 26% of papillary RCCs, and in only 6% of chromophobe RCC and 14% of oncocytomas. Within the clear cell carcinoma group, most positive cases (87%) demonstrated strong expression, whereas only 1 papillary RCC, 1 chromophobe RCC and none of the oncocytomas demonstrated strong immunoreactivity. In this study we used commercially available rabbit-antihuman GR polyclonal antibody PA1-511A from Affinity Bioreagents (Golden, CO) which recognizes both the -α and -β isoforms of GR. In order to recognize specific isoform expressed in RCC, we measured both isoforms by quantitative real-time PCR and demonstrated that RCCs express GR-α isoform. We found that GR expression is associated with tumors of low nuclear grade (Fuhrman grade 1 and 2) and low stage (stage 1 and 2). Although GR expression was demonstrated predominantly in clear cell RCC group, the loss of GR expression in high-grade tumors and overlap with other histologic subtypes of RCCs limit the diagnostic utility of this marker. GR appears to be a marker of less aggressive behavior in RCC as there is significant correlation between GR expression and overall survival in RCC. By the end of follow-up 86% of CRCC patients with tumors expressing GRs were alive as compared to 54% of patients whose tumors were negative.

Since GRs are cytoplasmic receptors, which are translocated to the nuclei upon activation, the predominantly nuclear immunoreactivity of GRs suggests that these receptors are activated in RCCs. Association of GR expression with less aggressive behavior also suggests the tumor-suppressive role of GRs. Signaling through GRs in renal cancer cells involves suppression of other transcription factors, including nuclear factor *k*B, AP-1, CREB, CCAAT enhancer binding protein (C/EBP), signal transduction activator of transcription (STAT), p53, Smad, *etc* (De Bosscher et al. 2003). Treatment of RCC cell lines with glucocorticoids (dexamethasone) inhibits the activation of nuclear factor kB and its downstream products including IL-2, IL-6, IL-8, and vascular endothelial growth factor which have been demonstrated to promote growth of RCC cell lines (Arai et al. 2008; Iwai et al. 2004; Miki et al. 1989; Takenawa et al. 1995). Glucocorticoids have long been used as anti-inflammatory drugs, and have been beneficial in the treatment of hematopoietic neoplasms (multiple myeloma) and solid malignancies such as hormone-refractory prostate cancer (Greenstein et al. 2002; Storlie et al. 1995). Although glucocorticoids have not been implicated in the treatment of patients with renal cancer, there are few case reports describing the beneficial effects of incidental glucocorticoid treatment in metastatic RCC (Christophersen et al. 2006; Omland & Fossa 1989; Tanaka et al. 2003). Palliation treatment with oral dexamethasone was associated with complete regression of pulmonary and brain metastases (Omland & Fossa 1989). In another case, multiple lung and bone metastases of RCC completely

regressed after palliative treatment with betamethasone (Tanaka et al. 2003). A 10 year complete remission of metastatic RCC to the liver and retroperitoneal lymph nodes was described in a patient who received palliative cortisone therapy (Christophersen et al. 2006). The mechanism of metastases regression in these cases is unknown and is not likely to be immune related, because glucocorticoids are known to suppress the immune system. These observations suggest that GR and its agonists may have a potential role in novel anti-cancer hormonal therapies in clear cell RCC.

3. Mineralocorticoid receptor

The mineralocorticoid receptor (MR) has long been considered as a secondary glucocorticoid receptor, even though specific roles of its natural ligand, aldosterone, have been well established since the purification of electrocortin more than 50 years ago. Aldosterone was initially restricted to the control of sodium reabsorption in the kidney, thereby being recognized as a major regulator of volume status and blood pressure. The cloning of a specific receptor for aldosterone (Arriza et al. 1987) definitively moved MR out of the shadow of GR and opened a new era of exciting biological, biochemical, and genetic studies that have provided important insights into the complexity of MR action. The MR is closely related to GR and is 94% homologous in the DNA binding domain and 57% homologous in the ligand binding domain, but only 15% homologous in the N-terminal region (Evans 1988). The MR has a similar affinity for the mineralocorticoid aldosterone and the glucocorticoids corticosterone and cortisol (Krozowski & Funder 1983). Although rats and mice synthesize only corticosterone, cortisol is the predominant glucocorticoid in humans and many other mammals, including rodents. Since the circulating levels of glucocorticoids are several orders of magnitude higher than those of aldosterone, the primary mineralocorticoid, glucocorticoid activation of MR may be functionally significant. Specificity is conferred by the enzyme 11β-hydroxysteroid dehydrogenase type II (11β-HSD2) which converts the cortisol to the less active compound cortisone, thus allowing aldosterone binding to MR. In the absence of ligand, MRs are located in both the cytosol and nucleus bound by a variety of chaperone proteins, including hsp90. Upon exposure to either aldosterone or corticosterone, most MRs are found in the nucleus, where they bind to hormone-response elements and mediate gene expression of signaling proteins regulating water and electrolyte transport including K-ras, serine-threonine kinase Sgk1, and corticosteroid hormone-induced factor (Connell & Davies 2005). The most recent role of aldosterone in renal and cardiac fibrosis has indicated a pro-fibrotic role for MR and the product of 11β-HSD2, cortisone or 11-dehydro-corticosterone in the regulation of this process (Brem et al.).

3.1 Expression of MR in the normal kidney

In contrast to GRs which are expressed in a broad variety of cells, expression of MRs is restricted to fewer cell types. The MR is expressed in so-called "classical" aldosterone target tissues, which are sodium-transporting epithelia (kidney, colon, pancreas, salivary, and sweat glands) and in a variety of non-epithelial target tissues such as the central nervous system, mononuclear lymphocytes, large blood vessels, and the heart (Arriza et al. 1987; Sasano et al. 1992). A general agreement exists that the distal nephron is an aldosterone-specific target site. Specific nuclear binding sites for aldosterone exist from the thick

ascending limb of Henle's loop (cortical part) to the distal collecting duct in rabbit and rat kidneys (Farman & Bonvalet 1983; Farman et al. 1982). MR is expressed in the distal tubules, the connecting tubules, and along the collecting ducts at the mRNA level in rat and rabbit kidneys (Escoubet et al. 1996; Todd-Turla et al. 1993) and at the protein level in rabbit kidneys (Lombes et al. 1990). Immunohistochemical studies showed that in normal human kidney MR is expressed in the distal convoluted tubules, collecting ducts, and loops of Henle with predominant nuclear localization (Hirasawa et al. 1997; Sasano et al. 1992; Yakirevich et al. 2008).

3.2 Expression of MR in kidney tumors

More than 30 years ago Rafestin-Oblin et al. demonstrated the presence of high-affinity sites for aldosterone in normal human kidneys using a ligand-binding assay. In RCCs the cytosol and nuclear aldosterone binding was significantly lower than in normal tissues (Rafestin-Oblin et al. 1979). However, this study focused exclusively on clear cell RCCs. Recently using immunohistochemistry we analyzed tissue microarray specimens from patients with different histologic subtypes of renal cell neoplasms, and in addition, we quantitated MR mRNA by real time RT-PCR (Yakirevich et al. 2008). Most of the chromophobe RCC (90%) and oncocytomas (93%) strongly expressed MR. No MR immunoreactivity was detected in clear cell RCC, including clear cell carcinoma with predominantly granular cytoplasm, or in papillary RCC. The MR+ immunophenotype of chromophobe carcinoma and oncocytoma reflects their histogenetic origin from phenotypically similar distal convoluted tubules and collecting ducts, whereas absence of immunoreactivity in clear cell RCC is consistent with its origin from proximal convoluted tubules. As we described in the previous section, proximal tubules and histogenetically related clear cell RCCs express high levels of GR. MR appears to be a sensitive and specific marker of the distal nephron and its related neoplasms (chromophobe RCC and oncocytoma) and may be considered in the immunohistochemical panel to more accurately subtype renal cell tumors.

4. Estrogen receptor

The effects of estrogens are mediated by estrogen receptors (ERs). ERs were discovered in the 1960's by Jensen and Jacobson (Jensen et al. 2010). The basic structure of ER protein is similar to other steroid receptors and contains a DNA binding domain, transcription modulating domain, and steroid hormone binding domain. There are two ER types encoded on different chromosomes: ER-α cloned in 1986 and ER-β, which was discovered in 1996 (Greene et al. 1986; Kuiper et al. 1996). ER-α is expressed in a variety of human organs, mainly reproductive, including the mammary gland, ovary, uterus, and vagina (Muramatsu & Inoue 2000). ER-β is expressed in genitourinary human tissues such as prostate, ovary, testis, bladder, uterus, and renal pelvis, in the central nervous system, and is especially increased compared to ER-α in various fetal tissues such as adrenals (Gustafsson 1999). The affinity of ER-β to bind estradiol-17β is similar to the ER-α form. However, ER-β binds both androgens and phytoestrogens with greater affinity. The main physiologic role of ERs is implicated in the control of proliferation, differentiation, and development of many tissues. In contrast to the beneficial physiologic effects, ERs may also promote the development and growth of variety of cancers, including breast, endometrial and ovarian carcinomas in humans (Speirs et al. 1999) and renal tumors in Syrian hamsters (Li et al. 2001).

4.1 Expression of ER in the normal kidney

Expression of ERs was extensively studied in hamster kidneys; however, the distribution of ER in normal hamster kidney is controversial. In a study by Bhat et al. who treated hamsters with estradiol to induce tumors, ER immunolocalization in normal kidneys of estrogen-treated hamsters or in untreated controls was identified only in the renal glomerular pododcytes, mesangial and parietal cells and in several interstitial cell types but not in the tubular epithelia of the cortex (Bhat et al. 1993). In addition, arterial cells, including pericytes and endothelial cells of the arteriolae rectae and endothelial cells of the arterial vasa recta, strongly expressed ER. The receptor distribution in kidneys of untreated female hamsters matched that of males, but the intensity of staining was higher than in male kidneys. Another study confirmed immunohistochemical expression of ER in interstitial cells and localized these cells to the corticomedullary junction (Li et al. 2001). The authors found that estrogen treatment causes a significant increase in ER-α positive interstitial cells compared to untreated controls and hypothesized that renal tumors arise from a subset of multipotential interstitial cells driven to proliferate by estrogens. However, in contrast to the study by Bhat et al., in this study ER expression was consistently demonstrated in nuclei of proximal tubules and disappeared after estrogen treatment.

4.2 Expression of ER in kidney tumors

Initial biochemical studies of ER status in renal tumors were performed in early 1980s by the dextran-coated charcoal method and the sucrose gradient centrifugation assay. These biochemical assays were based on cytosol preparations containing high, but unknown levels of plasma contamination. Furthermore, there was significant inconsistency in the number of tumor cells present within the specimens (Karr et al. 1983). Therefore, the level and frequency of ER expression in human kidney tumors were highly variable. Hemstreet et al. reported detectable ERs in 30% of the tumors compared to 40% of normals, whereas in other studies utilizing similar biochemical techniques ERs were not detected or detected in a rather low percentage of 4-9% of tumors (Hemstreet et al. 1980; Karr et al. 1983; Pearson et al. 1981). In a more recent immunohistochemical analysis of steroid hormone expression in tissue microarrays containing 182 RCCs of different histologic subtypes, Langer et al. demonstrated ER immunoreactivity in less than 10% of tumor cells in only 2 of 182 of patients (1.1%), including one clear cell RCC and one chromophobe RCC (Langner et al. 2004). Thus, the biochemical and immunohistochemical results provide evidence that ER is not expressed or very rare expressed in low levels in RCCs.

Recently, several benign renal tumors, characterized by the presence of stroma that resembles ovarian, endometrial, and mullerian-like, have been described, including cystic nephroma, mixed epithelial and stromal tumor (MEST) and angiomyolipomas with epithelial cysts (AMLEC) (Fine et al. 2006; Turbiner et al. 2007). Adsay et al. detected ERs in nuclei of the spindle cells in seven of 12 MESTs (Adsay et al. 2000). The staining was strong and diffuse and was present predominantly in the areas with long, slender, fibrocyte-like cells. In three of these cases, the epithelial cells also exhibited a cytoplasmic reaction with antibody to ER. Distinctive clinical and pathologic features characterize these lesions. Most of the patients in study of Adsay et al. were middle-aged (perimenopausal) females (mean age, 56 years) who had a long-term history of estrogen use. The only male patient also had a history of diethylstilbestrol exposure for 7 years followed by 4 years of lupron therapy for

prostatic adenocarcinoma. These clinical findings, combined with frequent ER expression detected by immunohistochemistry raise the possibility of hormonal mechanism of pathogenesis of these tumors. It is plausible that the spindle cells of these tumors arise from a "periductal fetal mesenchyma" present in epithelial structures of organs such as kidney, pancreas, and liver. The primitive mesenchyme may have the capacity to interact with epithelia. Alterations of hormonal milieu (perimenopausal changes or therapeutic hormones with unopposed estrogens) may induce proliferation of this mesenchyme, which in turn activates the growth of epithelial component.

5. Progesterone receptor

The progesterone receptor (PR) has two predominant isoforms: PR-α, and PR-β, which are produced from a single gene by alternative promoter usage (Jeltsch et al. 1986). These isoforms have similar steroid hormone and DNA binding activities, but PR-β has a much higher transcriptional activating potential. Clinically, PR expression is routinely assessed by immunohistochemistry using an antibody that recognizes both PR-α and PR-β.

5.1 Expression of PR in the normal kidney

No detectable PR staining was seen in renal sections from untreated castrated male hamsters in a study by Bhat et al. (Bhat et al. 1993). However, after estrogen treatment, PR expression was detected in single interstitial cells. The pattern of PR immunoreactivity was largely confined to interstitial cells located at the renal corticomedullary region, similar to ER expressing cells described above. PRs were identified in normal human kidneys by biochemical and more recently immunohistochemical techniques (Hemstreet et al. 1980; McDonald et al. 1983). Interesting, in normal human kidneys PRs were detected by immunohistochemistry in interstitial stromal cells, some tubules, and mesangial cells of glomeruli in two of seven cases (Tickoo et al. 2008).

5.2 Expression of PR in kidney tumors

Expression of PR in kidney tumors was studied in parallel with ER analysis. The level and frequency of PR in human kidney tumors is highly variable when analyzed biochemically varying from 0 to 23% (Hemstreet et al. 1980; Karr et al. 1983; Pearson et al. 1981). Immunohistochemical analysis of steroid hormone expression in tissue microarrays containing 182 RCCs of different histologic subtypes demonstrated PR immunoreactivity in less than 10% of tumor cells in only two of 182 patients, including one clear cell RCC and one papillary RCC (Langner et al. 2004). PRs were found in stromal cells of renal neoplasms with ovarian-like stroma, although less frequently as compared to ER (Adsay et al. 2000). More recently Mai et al. identified PR immunoreactivity of tumor cells and stromal cells within the neoplasm and/or surrounding capsule in renal oncocytoma and chromophobe RCC (Mai et al. 2008). This immunoreactivity was not seen in other tumors with oncocytic/eosinophilic cytoplasm, such as papillary RCC with eosinophilc cytoplasm or clear cell RCC with eosinophilic cytoplasm. PR appears to be a sensitive and highly specific marker for renal oncocytoma and a highly specific marker for chromophobe RCC. It was demonstrated that PR immunoreactivity is more extensive in oncocytoma than in chromophobe RCC, therefore, the extent of PR immunoreactivity could be useful in

distinguishing oncocytoma from chromophobe RCC. The presence of PR in oncocytoma and chromophobe RCC provides additional support to the histopathogenetic relationship between renal oncocytoma and chromophobe RCC.

6. Androgen receptor

Androgens are essential for differentiation and growth of male reproductive organs and for various biological effects in the kidney, brain, liver, muscle, bone and skin. Androgens include testosterone and dihydrotestosterone and mediate their biologic effect through the androgen receptor (AR). The *AR* gene is located on chromosome Xq11-12 (Brown et al. 1989; Lubahn et al. 1988). Males have a single copy of the gene allowing phenotypic manifestation of any genetic alteration. Transcription of the *AR* gene is cell-specific and modified by age, androgen and other steroid hormones (Gelmann 2002). Androgen is best known to influence development and growth of prostate cancer. However, its metabolic role in cancer is not limited to the prostate and a number of studies utilizing animal models combined with clinical and epidemiologic data suggest a role for androgen in RCC (Concolino, Marocchi, Conti et al. 1978; Karr et al. 1983).

6.1 Expression of AR in the normal kidney

AR is ubiquitously expressed in the whole body with studies showing detectable levels of protein and mRNA in adrenal glands, uterus, aorta, adipose tissue, kidney, spleen, heart, lung, large intestine, stomach, small intestine and liver (Kimura et al. 1993; Ruizeveld de Winter et al. 1991; Takeda et al. 1990). In normal kidneys AR expression was consistently demonstrated to be present in the nuclei of distal tubule cells (Kimura et al. 1993; Li et al. 2010). Additionally, a study by Takeda et al. showed AR immunoreactivity not only in the distal tubule but also in the proximal tubule and focal parietal expression in the Bowman's capsule (Takeda et al. 1990).

6.2 Expression of AR in kidney tumors

The hormone dependence of RCC has been established in animal models and in humans for many years (Bloom 1973; Concolino, Marocchi, Conti et al. 1978; Concolino, Marocchi, Tenaglia et al. 1978; Li et al. 1977). In humans, extensive research on AR in RCC has shown variable results (Concolino et al. 1981; Jakse & Muller-Holzner 1988; Karr et al. 1983; Klotzl et al. 1987; Nakano et al. 1984; Noronha & Rao 1985) In a case series study by Brown et al., that included 12 primary clear cell RCCs and 5 clear cell RCCs metastatic to the central nervous system, AR immunoreactivity was present in five primary and one metastatic RCC (Brown et al. 1998). A more recent study by Langner et al. demonstrated that AR immunoreactivity was not detectable in non-tumoral kidney tissue (Langner et al. 2004). However, AR was found in 15% of patients with RCC and inversely correlated with histopathologic stage, with 27% of pT1 tumors being positive versus 4% of pT3 tumors. Furthermore, expression of AR was higher in pT1a tumors compared to pT1b (32% vs. 17%). Additionally, AR expression inversely correlated with nuclear grade with 21% positivity in nuclear grades 1 and 2 and 7% in nuclear grades 3 and 4. Univariate analysis showed a longer disease free survival in patients with AR positive tumors compared to patients with

AR negative tumors (Langner et al. 2004). These results reflect similar trends observed with GRs in RCC (Yakirevich et al. 2011), however, the diagnostic, prognostic or therapeutic utility of AR analysis in RCC is uncertain and might require further investigations.

7. Vitamin D receptor

Vitamin D is a lipid-soluble compound whose major function is the maintenance of adequate plasma levels of calcium and phosphorus, important for bone mineralization, neuromuscular transmission and general cellular metabolism. Vitamin D receptor (VDR) is present in various tissues that do not participate in calcium metabolism and regulates the expression of hundreds of genes that control cell proliferation, differentiation and angiogenesis. Low levels of vitamin D have been associated with increased incidence of colon, prostate and breast cancer (Thacher & Clarke 2011). Recent studies suggest that vitamin D may be inversely associated with the risk of RCC. (Bosetti et al. 2007; Ikuyama et al. 2002; Karami et al. 2008; Obara, Suzuki et al. 2007). Vitamin D receptor is expressed in malignant tumors, including RCC, and mediates the biological actions of $1,25(OH)_2D_3$ (Lamprecht & Lipkin 2003). In this section, we will review the current literature on the relevance of vitamin D and its receptor in RCC.

7.1 Expression of VDR in the normal kidney

The kidney is a major organ for vitamin D metabolism and calcium homeostasis. Activation of vitamin D involves conversion of 7-dehydrocholesterol to cholecalciferol by UVB radiation in the skin. Cholecalciferol is metabolized by the 25-hydroxylases (CYP2R1 and CYP27A1) in the liver to 25-hydroxycholecalciferol ($25(OH)D_3$). $25(OH)D_3$ then undergoes glomerular filtration and is subsequently converted to the active form calcitriol ($1,25(OH)_2D_3$) by the 1α-hydroxylase (CYP27B1) located primarily in the proximal tubule. Calcitriol binds to an intracellular receptor (VDR), a ligand dependent transcription factor belonging to the class II nuclear receptor subfamily. The effect of calcitriol is negatively controlled by CYP24A1 (Fleet 2008; Nykjaer et al. 1999). Immunohistochemistry studies of non-tumoral kidney show expression of VDR predominantly in the distal tubules and collecting ducts with only faint or lack of stain in the proximal tubule cells (Blomberg Jensen et al. 2010; Liu et al. 2006; Obara, Konda et al. 2007). This expression pattern is consistent with studies that demonstrate that vitamin-D induced calcium re-absorption occurs in the distal tubules (Li & Christakos 1991).

7.2 Expression of VDR in kidney tumors

In keeping with absence of VDR expression in the proximal tubule, a study by Liu et al. showed that clear cell RCC is generally negative for VDR by immunohistochemistry and showed decreased mRNA level compared to non-tumoral kidney control tissue by RT-PCR (Liu et al. 2006). When whole sections of tumors were stained, expression of VDR was present only focally in the peripheral region of the tumor. Previously, a study by Madej et al. showed that expression of VDR in clear cell RCC was similar to control tissue by Western and Northern blot analysis (Madej et al. 2003). This discrepancy could be due to a difference in the degree of differentiation of the tumors analyzed in each study. While the expression

level seems not to be affected by the Fuhrman nuclear grade, increased VDR immunoreactivity was observed in sarcomatous and poorly differentiated areas of RCC and in metastatic tumors or in intravascular tumor islands (Liu et al. 2006).

A different study by Blomberg Jensen et al. showed that VDR mRNA was detected in all normal kidney samples while almost undetectable in clear cell RCC with similar results confirmed by Western blot (Blomberg Jensen et al. 2010). Additionally, in this study, the authors investigated the expression of Vitamin D activating enzymes including CYP2R1, CYP27A1, and CYP27B1. The 1 α-hydroxylase (CYP27B1) was present in all normal samples with varying degrees of expression levels, the lowest expression in atrophic kidneys. By immunohistochemistry and in-situ hybridization, expression of CYP2R1 and CYP27A1 was localized to the distal tubule, collecting ducts and minimal expression in the proximal tubule. Expression of CYP27B1 was more prominent in the proximal tubule. Expression of these enzymes was diminished in clear cell RCC along with decreased expression of VDR (Blomberg Jensen et al. 2010). Papillary RCC is positive for VDR in the great majority of cases. This recapitulates more closely the phenotype of distal tubules. Similarly, chromophobe carcinoma and oncocytomas are also positive for VDR. Staining of chromophobe carcinoma accentuates the cell membrane while in oncocytomas it is stronger in the perinuclear area (Liu et al. 2006). Collecting duct carcinoma is thought to derive from the principal cells of the collecting duct of Bellini. Consistent with other tumors of origin from the distal nephron, three out of three collecting duct carcinomas tested were positive for VDR by immunohistochemistry (Liu et al. 2006).

Currently, immunohistochemistry for vitamin D is not routinely used for diagnostic purposes. However, several findings described above could eventually prove to have diagnostic utility in anatomic pathology. Because almost all clear cell RCC proved to be negative by immunohistochemistry (with the exception of some high grade tumors, or tumor present within vascular lumens), a positive VDR immunohistochemistry result should alert the pathologist about a potential problem in the classification of a tumor thought to be clear cell RCC (Liu et al. 2006).

A frequent problem in the diagnosis of renal tumors is the distinction between oncocytomas and eosinophilic chromophobe carcinoma (Takahashi et al. 2003; Young et al. 2001). This distinction is critical as these tumors have completely different prognostic and therapeutic clinical implications. Results reported in the literature indicate that both tumors are immunoreactive for VDR with a difference in the localization of the stain. While oncocytomas stained preferably in the perinuclear area, chromophobe carcinoma showed accentuated stain of the cell membrane (Liu et al. 2006).

Positive stain for VDR in papillary RCC could help differentiate this tumor from clear cell RCC with papillary features, which will be negative in the great majority of cases. VDR expression in CPRCC has not been tested; however, since these tumors are CK7 positive, it is likely that they are VDR positive as well, consistent with distal nephron phenotype. Only three cases of collecting duct carcinoma have been tested for VDR immunoreactivity and all of them turned positive. Differential diagnosis of these tumors could be challenging due to their infrequent presentations. Main differential diagnoses include adenocarcinoma or urothelial carcinoma with glandular differentiation. Although there is lack of information in

the literature regarding expression of VDR receptor in urothelial carcinoma with glandular differentiation, studies on normal urothelium and urothelial neoplasms have shown consistent positivity for VDR for which it seems unlikely that it would have utility in the differential diagnosis on this context (Hermann & Andersen 1997; Konety et al. 2001).

The anti-cancer effect of vitamin D includes inhibition of cell proliferation and induction of apoptosis (Blutt et al. 2000; Rashid et al. 2001; Zhuang & Burnstein 1998). Expression of VDR as detected by immunohistochemistry was not associated with survival in a cohort of 68 RCC patients (Obara, Konda et al. 2007). This could be due to a small number of patients studied or secondary to other possible alterations within the signaling pathway that could interfere with the normal function of the receptor. Different studies have shown consistently that VDR-DNA complexes are decreased in RCC, even in the presence of exogenous vitamin D (Madej et al. 2003; Trydal et al. 1988). This functional impairment could be secondary to suboptimal VDR heterodimerization with its partners in tumor cells. Before binding to DNA, VDR heterodimerizes with retinoid X receptor (RXR), its obligate partner (Barsony & Prufer 2002; Prufer & Barsony 2002). Retinoid X receptors are part of the retinoic acid receptor systems and share with retinoic acid part of the signaling pathways. Notably, positive RXR-γ staining in RCC correlates with prolonged overall 5-years survival (Obara, Konda et al. 2007).

Calcitriol has anti-proliferative properties in a variety of malignant cell types (Getzenberg et al. 1997; Reichel et al. 1989). The anti-neoplastic activity of VDR ligands was first described in 1981 in a study showing differentiating properties of calcitriol in mouse myeloid leukemia cells (Abe et al. 1981). Since then, a number of studies have demonstrated the in-vitro and in-vivo anti-cancer potential of vitamin D in models of bladder, breast, colon, endometrium, lung, pancreas, prostate and squamous cell carcinoma, sarcomas of the soft tissues and bone, neuroblastoma, glioma, melanoma, and other malignancies (Beer & Myrthue 2004; Trump et al. 2004; Trump et al. 2006).

Calcitriol treatment of cells inhibited cell growth and clonogenicity of the RCC cell line derived from a pulmonary metastasis of RCC, (Nagakura et al. 1986). In a different study, BALB/c mice were inoculated with murine renal cancer Renca and graded doses of calcitriol were given intraperitoneally. Vitamin D inhibited tumor growth and prolonged the life span of Renca-bearing mice in a dose-dependent manner. Furthermore, vitamin D treated mice showed reduced pulmonary and hepatic metastates (Fujioka et al. 1998). Despite these and other promising results in cell culture and in murine models, the utility of vitamin D therapy in humans has been challenged by its hypercalcemic toxic effect (Fakih et al. 2007; Muindi et al. 2009). To try to bypass this toxicity, researchers have explored alternative vitamin D like molecules. A recent published study investigated the in-vitro and in-vivo effect of 1,25-dihydroxyvitamin D3-3-bromoacetate [1,25$(OH)_2$D3-3-BE], an alkylating derivative of 1,25$(OH)_2$D3 (Lambert et al. 2010). This study reports that 1,25$(OH)_2$D3-3-BE is significantly more potent than an equivalent concentration of 1,25$(OH)_2$D3 in inhibiting growth of A498 and Caki 1 human kidney cancer cells. The mechanisms behind cell growth inhibition of cell-cycle progression include downregulating cyclin A and induction of apoptosis through caspase activity. When compared to calcitriol, 1,25$(OH)_2$D3-3-BE was more potent at reducing tumor size, which was accompanied by an increase in apoptosis

and reduction of cyclin A staining in the tumors. These results show a promising potential of vitamin D derived compounds as targeted therapy for RCC patients (Lambert et al. 2010).

8. Retinoic acid receptors

Retinoids are a family of molecules related to vitamin A that include retinoic acid (RA) and all-trans retinoid. Retinoids participate in diverse functions in many organ systems during development and in adulthood including vision, neural function and immune response. Extensive research also supports a role of retinoids in cell proliferation and differentiation through cell cycle signaling promoting block in G1 phase of cell cycle, by directly or indirectly modulating cyclins, CDKs, and cell-cycle inhibitors (Mongan & Gudas 2007; Tang & Gudas 2011). There are two distinct retinoid nuclear receptor systems, the RARs types -α, -β and -γ, and RXRs types -α, -β and -γ (Pemrick et al. 1994). RARs form heterodimers with RXRs and act by binding to retinoic acid response elements (RARE) located in the promoter regions of RA-target genes and modulate transcription rates (Altucci & Gronemeyer 2001). In addition to its role in senescence and cell differentiation, retinoic acid can follow an alternative pathway by binding to a so-called orphan nuclear receptor, PPAR-β/-δ to promote cell survival under certain conditions (Schug et al. 2007).

8.1 Expression of retinoic acid receptors in the normal kidney

Studies evaluating the expression of RARs and RXRs indicate that expression of a given receptor subtype is cell type specific and that retinoic acid effect in different cell types are linked to specific receptor type (Geradts et al. 1993; Kakizuka et al. 1991; Moasser et al. 1994; Moasser et al. 1995; Sheikh et al. 1994; Swisshelm et al. 1994). Information on expression of RARs in normal kidney derives primarily from normal controls used in studies for various purposes. RAR-β mRNA has consistently been found to be expressed in normal kidney tissue samples (Goelden et al. 2005; Vanderleede et al. 1995). Additionally, expression of RARs and RXRs were studied in podocytes, which expressed most isoforms of retinoic acid receptors (RAR) and RXRs with the exception of RXR-γ (He et al. 2007). Obara et al. detected expression of RXR-α and-γ in nuclei of proximal tubule cells, while RXR-β expression was present in proximal tubule cells and interstitial cells (Obara, Konda et al. 2007).

8.2 Expression of retinoic acid receptors in kidney tumors

Dysregulation of each RA receptor has been found in association with different types of cancer. RAR-α is dysregulated in acute promyelocytic leukemia (APL). Majority of APL cases present a chromosomal translocation that fuses the promyelocytic leukemia gene, *PML* and the *RAR-α* genes [t(15;17)(22;q11.2-12)] which can be effectively treated and cured with a combination of retinoid and chemotherapy. In contrast to RAR-α, RAR-β is involved in solid tumorigenesis including RCC (Argiles et al. 1994; Berg et al. 1999; Goelden et al. 2005; Hoffman et al. 1996). The RAR-β gene maps on the short arm of chromosome 3, a region frequently deleted in cancer (Houle et al. 1993). Several studies demonstrated decreased or undetectable levels of RAR-β mRNA in tissue or cell lines derived from different tumors including lung (Suh et al. 2002; Zhang et al. 1994), prostate (Nakayama et al. 2001), breast (Swisshelm et al. 1994), ovary (Sabichi et al. 1998), colon (Cote et al. 1998), head and neck

(Xu et al. 1994) and cervix (Geisen et al. 1997). RAR-β mRNA was decreased or not detectable in 11 of 12 RCC cell lines (Hoffman et al. 1996). These cell lines were either resistant or minimally inhibited when treated with 13-*cis*-RA (13-CRA). Conversely, chromophobe RCC shows much higher levels of expression of RAR-β with a ratio of tumor/normal of over 36 (Goelden et al. 2005). In clear cell RCC, immunoreactivity for RXR-α was observed in up to 70% of the cases, RXR-β was present in 47% of cases, and RXR-γ stain was seen in 85% of cases, in a study that included 49 CRCCs (Obara, Konda et al. 2007). Only expression of RXR-γ was found to correlate inversely with pathological and clinical stage. While all subtypes of RXRs showed variable nuclear or cytoplasmic stain, subcellular location did not correlate with any prognostic variables. Additionally, this study suggests a prolonged overall 5-year survival of patients with tumors that are RXR-γ positive (Obara, Konda et al. 2007).

In clinical trials, the effect of RA in RCC patients has been tested in patients with metastatic disease. A randomized clinical trial of 284 patients evaluated response to treatment with IFNα2a plus 13-cis-retinoic acid (13-CRA) or treatment with IFNα2a alone (Motzer et al. 2000). This study showed no difference in the overall survival but median duration of response (complete and partial combined) in the group treated with the combination was 33 months versus 22 months for the second group. Nineteen percent of patients treated with IFNα2a plus 13-CRA were progression-free at 24 months, compared with 10% of patients treated with IFNα2a alone (Motzer et al. 2000). However, a separate clinical trial that involved 320 patients concluded that progression-free and overall survival for patients with progressive metastatic RCC treated with IFNα2a plus 13-CRA were significantly longer compared with patients on IFN alone (Aass et al. 2005). Another clinical trial that included three different treatment regimens: *a*) triple combination of IL-2, IFNα2a, and fluorouracil; *b*) triple combination of group *a* and additional 13-CRA; *c*) control group treated with IFN-α and vinblastine. Progression-free and overall survival were significantly longer in groups *a* and *b* but there was no significant survival advantage for patients receiving 13-CRA (Atzpodien et al. 2004). These studies suggest that there is some beneficial effect of retinoids treatment, in at least a subset of patients with RCC.

9. Conclusion

Steroid receptors are differentially expressed in the normal kidney and in renal cell neoplasms. Several steroid receptors, such as MR, PR, and vitamin D receptor may be included in diagnostic immunohistochemical panels in order to more accurately subtype renal cell tumors. Although ER is not detected in significant amounts in RCCs, it is expressed by stromal cells in several benign renal neoplasms and may be involved in their pathogenesis. GR and AR appear to be markers of less aggressive behavior in clear cell RCC. Finally, steroid receptors and their downstream signaling mechanisms may have a potential role in novel anticancer hormonal therapies in RCCs.

10. References

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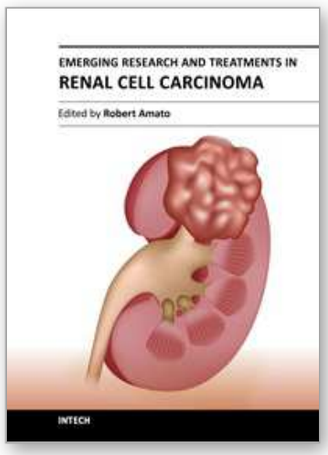

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