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Diana da Silva Fernandes

Pathology, therapy, and prognosis of papillary renal carcinoma

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Pathology, therapy, and prognosis of papillary renal carcinoma

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“Foi o tempo que dedicaste à tua rosa que a fez tão importante”

in Principezinho

Às únicas e mais belas rosas da minha vida, aos meus pais, à minha irmã, aos meus avós, aos meus padrinhos e ao meu namorado, muito obrigada pelo apoio incondicional que me deram.

Pathology, therapy, and prognosis of papillary renal carcinoma

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Summary: Papillary renal cell carcinoma (pRCC) accounts for about 10% of renal parenchymal tumors. There are two pRCC subtypes reported in several studies, but so far limited molecular evidence to validate this pRCC subtyping in daily routine.
In this review we summarize relevant knowledge on pRCC regarding clinical, treatment options, and tumor features: clinical presentation, histopathology, electron microscopy, immunohistochemistry, cytogenetics, and genetic/ molecular. Genetic and molecular features have been used to track new tumor markers which may eventually enable the identification of new therapeutic targets. We present an overview of currently available pRCC treatment options and some of the new promising agents. Specific prognosis features of pRCC remain controversial.

Keywords: papillary renal cell carcinoma; epidemiology; genetic; morphology; immunohistochemical; chromosomal; treatment; prognosis

1. Epidemiology

Kidney cancer is the 13th most common malignancy worldwide, with ~ 271 000 new cases diagnosed in 2008 and ~ 116 000 people die from the disease [1]. Renal cell carcinoma (RCC) comprises about 3% of all solid tumors [2]. In Europe ~ 88 400 new cases of kidney cancer occurred in 2008, the 10th most common cancer [1]. RCC is extremely rare in the pediatric population and accounts for ~ 6% of malignant pediatric tumors (‹ 4% of pediatric renal tumors) [3].

The incidence of kidney cancer varies geographically: highest in Europe, North America, and Australia and lowest in India, Japan, Africa, and China [1]. The Czech Republic, Lithuania, Latvia, Estonia, and Iceland have the highest RCC rates in Europe, while incidence is lowest in

Romania, Cyprus, and Portugal [4]. In 2008, decreased or stabilized incidence in northern Europe countries occurred, particularly in Sweden, and generally increased (except for women in the early 2000s) in Eastern Europe [5].

The mortality rates from kidney cancer in European Union (EU) peaked at 4.8/100 000 in 1990–1994, and declined to 4.1 (−13%) in 2000–2004 [5]. In women in the EU, the corresponding values were 2.1 and 1.8 [5]. In Portugal mortality rates in women declined (−14%) during 1990–2004 [5].

Papillary RCC (pRCC) comprises ~ 6-18% of kidney tumors in reported series [6]. It is the most common histologic subtype observed in pediatric RCC and it was reported in 18 % of dialysis patients with less than 10 years of treatment [3, 7]. Atypical cysts with extensive papillary hyperplasia are often the precursors of papillary renal adenoma and cancer in these patients [8]. In children it may arise in the setting of pre-existing neoplasm, including Wilms tumor, metanephric adenoma, and metanephric adenofibroma [9]. Approximately 20% of pRCC are discovered as incidental findings [6].

Vikram *et al.* reported that the range of age is in the third to eighth decades, and male-to-female ratio from 2:1 to 3.9:1 [2]. There are no reports on specific symptoms and signs of pRCC.

2. Lifestyle Risk Factors

Table 1 summarizes lifestyle risk factors and pRCC.

Associated Risk Factors	**Non-associated Risk Factors**	**Controversial Risk Factors**
Cigarette smoking **ACDK**	**Obesity**	**Hypertension** **Animal products intake** **Fat intake**

Table 1 – Life Risk factors and papillary RCC. Acquired Cystic Disease- associated RCC (ACDK).[1, 7, 10-14]

3. Genetic syndromes

Table 2 summarizes genetic syndromes associated to pRCC.

Syndrome	Gene/location	Gene product	Papillary RCC	Other tumors/lesions
HPRCC	*MET*, 7q31.3; frequently exons 17, 18 and 19; occasionally exon 16	MET	Type 1: multiple, bilateral and multifocal	Breast, pancreas, lung, skin, and stomach tumors
HLRCC	*FH*, 1q42-44	FH	Type 2: unilateral, solitary, aggressive; metastasis (~20% HLRCC families)	Uterine and cutaneous leiomyoma/leiomyosarcoma
PTEN-HTS	*PTEN*, 10q23	PTEN	Unifocal	Cerebellar dysplastic gangliocytoma, breast, thyroid (nonmedullary) and endometrial tumors, hamartomatous intestinal polyps, lipomas, fibromas
BHD	*FLCN* (BHD), 17p11	Folliculin	Multiple and bilateral	Fibrofolliculoma, trichodiscoma, acrochordon, colon and kidney tumors
HPTJT	*CDC73* (*HRPT2*), 1q21-31	Parafibromin	Bilateral	Renal hamartoma, nephroblastoma, uterine tumor, parathyroid tumor, fibro-osseous mandibular and maxillary tumor
FPTC	Unknown gene, 1q21	Unknown	Multifocal	Renal adenoma and oncocytoma, papillary thyroid cancer, nodular thyroid disease

Table 2 – Inhered papillary RCC. Hereditary papillary RCC (HPRCC); Hereditary leiomyomatosis RCC (HLRCC); Phosphatase and tensin homolog (PTEN); PTEN hamartoma tumor syndrome (PTEN-HTS); Birt-Hogg-Dubé syndrome (BHD); Folliculin gene (*FLCN*); Hyperparathyroidism-jaw tumor syndrome (HPTJT); Familial papillary thyroid cancer (FPTC); Met proto-oncogene (MET); Fumarate hydratase (*FH*); Cell division cycle 73 (*CDC73*); Hyperparathyroidism 2 (with jaw tumor) HRPT2. [15-28]

In 1994 hereditary papillary renal cancer (HPRC) was reported as a rare autosomal dominant inherited syndrome with very high penetrance (30 families described so far), meaning that there is a high probability of a person developing pRCC by age 80 [16-18, 20, 29]. An early onset-form has been recently reported in which the disease appears in the second and third decade [29]. Diagnosis of this condition is based on the detection of germline mutation of the *c-MET* gene; c-*MET* mutations were reported to play a role in 13% of patients with pRCC and no family history of renal tumors [15, 16, 19, 30] (Table 1). Mutations of *c-MET* were also reported in a subset of tumors from patients with sporadic type 1 pRCC [31].

Hereditary leiomyomatosis RCC (HLRCC) mean age is 36–39 years, although the youngest age at diagnosis of pRCC in a fumarate hydratase (*FH*) gene mutation carrier was reported in a 11-year-old patient [23, 24]. Among 89 cases reported in the literature, six (7%) were found in individuals younger than 20 years [25]. Two distinct *FH* mutations occurring in heterozygote (2bpdel, codon 181 and R300X) were reported in HLRCC families affected by renal cancer and uterine leiomyosarcoma [21]. The renal tumors associated to HLRCC tend to be hypovascular, solitary, and may metastasize early [17].

Biallelic inactivation of succinate dehydrogenase gene (*SDH*) was reported as a pathway in the pathogenesis of pRCC [32]. Malinoc *et al.* based on the study of a small series, estimate that 10% of individuals with *SDHC* gene mutation develop RCC (both clear and papillary type) [32].

4. Pathological features

4.1 Macroscopic, Microscopic and Ultrastructural features

Macroscopy [2, 33, 34]

. Well-circumscribed, frequently with thick fibrous capsule or pseudocapsule

. Mean size (range): 6.7-7.2 cm (1.2-26 cm)

. Small tumors are usually solid, and large tumors show frequent cystic change

. Yellow or brown cut surface

. Frequent hemorrhage (8% of the cases) and necrosis

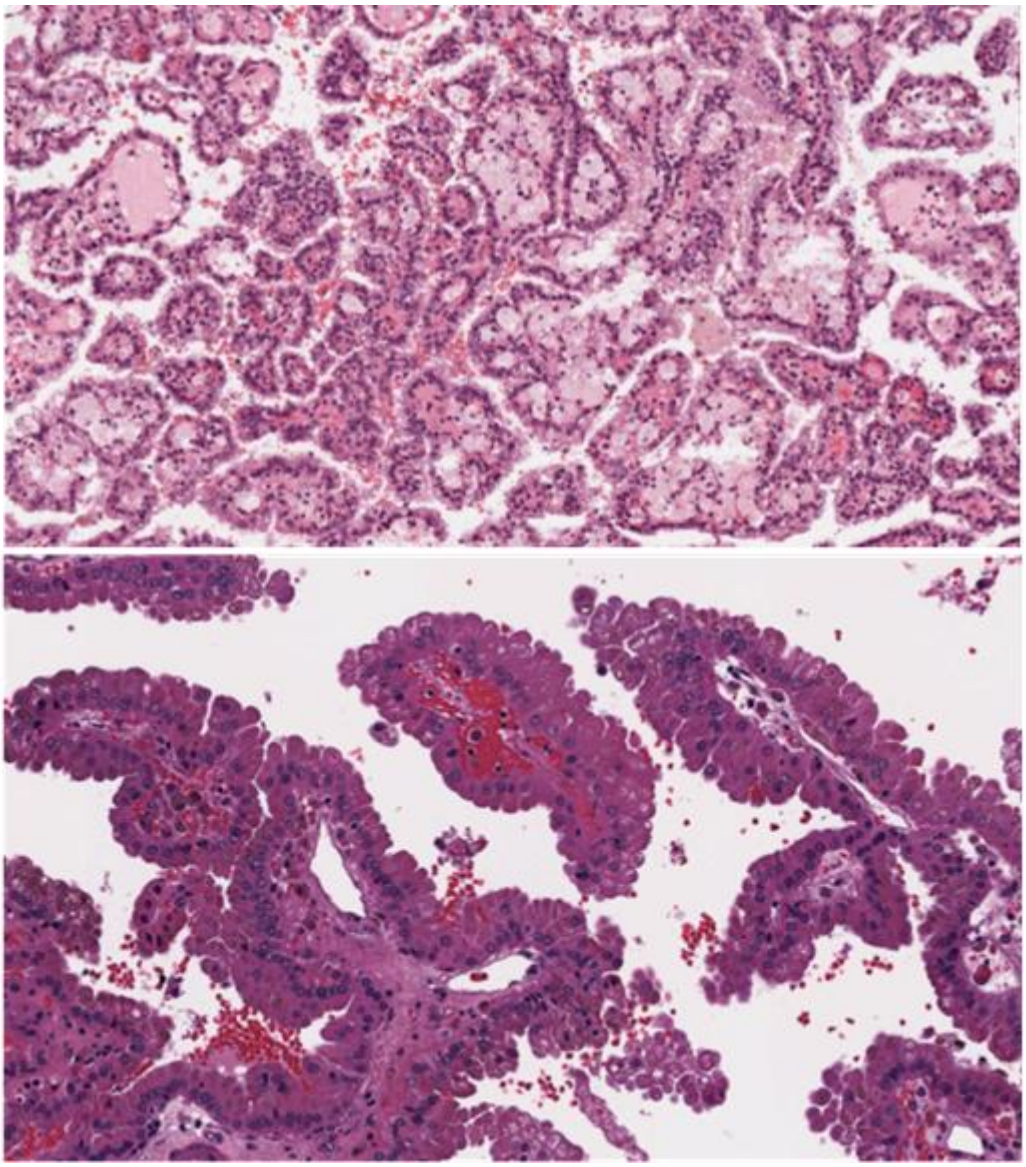
. Bilaterality (4%) or multifocality (22.5%) can occur.

Microscopy [2, 35, 36]

. Type 1 pRCC: small cuboidal or columnar cells with scant pale cytoplasm and hyperchromatic nuclei arranged on a single layer on basement membrane of papillary core; psammoma bodies, foamy macrophages, glomeruloid papillae; lower nuclear grade than type 2;

. Type 2 pRCC: large cells with abundant eosinophilic granular cytoplasm and grade 3 nuclei (prominent nuclei); pseudostratified nuclei; variable foam cells and necrosis.

Figure 1- Microscopic features of papillary RCC subtypes: A - Type 1 pRCC; B - Type 2 pRCC.



Ultrastructure [35]

. Type 1 pRCC: many glycogen granules, many secondary lysosomes containing lipid vacuoles, and few rough endoplasmic reticulum.

. Type 2 pRCC: many mitochondria, few lipid vacuoles, and many smooth endoplasmic reticulum.

In 1997, two consensus conferences, in Heidelberg, Germany, and Rochester, Minnesota, recognized the existence of benign papillary neoplasms of the renal tubular epithelium that are incidental findings, are much more common than clinically recognized pRCC [35]. At the Rochester conference it was recognized that there are no reliable histological differences between these small tumors and many clinically detected pRCC, and renal papillary adenoma was defined on the basis of size, less than 5mm, whereas larger tumors were classified as pRCC [35].

Classically, tumors have been classified as pRCC if papillary structures comprise at least 50% but a variety of other architectural patterns such as tubular, trabecular and solid were reported [15, 37]. Kovacs *et al.* suggested that more than 75% of the tumor being composed of papillary structures may be a better criteria for discriminating pRCCs from nonpapillary RCCs showing 3p deletions [37]. The presence of solid variants of pRCC that are composed of poorly formed papillae were reported and this group comprises at most <3% of all pRCC [15].

The morphologic classification of pRCC into type 1 and 2 tumors has been supported by several histologic studies, although there is relatively limited molecular evidence to substantiate this subtyping [38]. Type 2 pRCC is composed of at least two genetically distinct subtypes: one subtype (type 2A) resembles type 1 in terms of indolent tumor behavior, excellent survival, low tumor grade, similar expression profiles, immunoreactivity, and inferred cytogenetic profiles; the other subtype (type 2B) is an highly metastatic, aggressive cancer that is molecularly distinct from type 1 or 2A tumors [38].

4.2 Immunohistochemistry features

Table 3 summarizes common immunohistochemical markers in pRCC.

Immunohistochemical markers of papillary RCC		
AE1/AE3	100%	
p 504 s	89.3 -100%	Other types of RCCs are rarely positive.
VIM	85.7-100 %	
CK7	90 %	> 80% in type 1; 10-20% in type 2.
PAX 2	85 -92.9 %	
CD10	67-93%	
PAX 8	87.5 %	
CLDN1	76-86%	
MUC1	89%	Higher expression rates in type 1.
MYC	67% (type 2 pRCC); 13% (other pRCC subtypes)	High-grade type 2
TOP2α	0.12-95.01%	Higher expression rates in type 1 (0.12-95.01% *vs.* 0.57–36.98%) than in type 2, and high grade tumors.

Table 3: Common immunohistochemical markers of papillary RCC. pRCC (papillary RCC); Cytokeratin AE1/AE3 (AE1/AE3); α-Methylacyl CoA racemase (P504S); Vimentin (VIM); Keratin 7 (CK7); Paired box 2 (PAX2); cluster differentiation marker 10 (CD10); Paired box 8 (PAX8); Claudin-1 (CLDN1); Carbonic anhydrase IX (CA9); Mucin 1 (MUC1); V-myc avian myelocytomatosis viral oncogene homolog (MYC); Topoisomerase (DNA) II alpha (TOP2α). [15, 39-56].

Other immunohistochemical markers are expressed in pRCC but with less diagnosis impact than the immunohistochemical markers described on Table 3.

Cell cycle fraction (Ki-67 index) and cell cycle rate (AgNOR score) are different when comparing the two histologic types of pRCC: both mean AgNOR score and mean Ki-67 index seem to be significantly higher in type 2 tumors [57].

4.3 Fine needle aspiration (FNA) [58]

. Cells with moderate to scant cytoplasm

. Small and uniform nuclei, often with prominent nuclear groves

. Single and small nucleoli with mild to moderate hipercromasia and mild pleomorphism

. Low to moderate nuclear/cytoplasm ratio

. Foamy macrophages in the background

. Intracellular hemosiderin

. Psammoma bodies within the papillae, and in the background.

Cytological features that are highly sensitive for the diagnosis of pRCC include intracytoplasmic hemosiderin and foamy macrophages [58]. These findings, in combination with the presence of papillae, nuclear grooves, inconspicuous nucleoli, increased nuclear to cytoplasmic ratio, are helpful in the FNA diagnosis of pRCC [58].

The presence of unusually numerous balls or three-dimensional clusters of cells with smooth borders represent the fragmented tips of the papillae [58]. This appearance may be an artifact, but is reproducible and may be useful for the diagnosis [58].

5. Flow cytometry features

DNA aneuploidy was reported in 50% pRCC [15]. According to del Vecchio *et al.* diploid and aneuploid patterns occur in 35% and 65% of tumors, respectively [59]; a strong correlation between nuclear grade and stage, as well as between nuclear grade/stage and ploidy pattern; and a strong correlation between nuclear grade/stage, ploidy pattern and clinical outcome.

6. Chromosomal analysis

Hierarchical clustering suggested two cytogenetic patterns that were reported to be common but not restricted to type 2 pRCC; one was characterized by combined high-level gains (ratios ≥2) of various chromosomes, including those commonly gained as primary and secondary

aberrations, and another by weakly correlated patterns of less common secondary chromosomal losses (ratios ≤1), including losses at 17p; there are increased numbers of chromosomal abnormalities in type 2 tumors [60] (Table 4).

Chromosomal Abnormalities in papillary RCC		
Observation	**Description**	**Comment**
Trisomy 7		80 % display copy number gain of the long arm of chromosome 7: 67% low-grade and 43% high-grade pRCC. Less number of cells with trisomy 7 in larger tumors.
Trisomy 17	80% of pRCC	The number of cells with trisomy 17 seems to increase with tumor growth; additional gains of chromosomes 12, 16, or 20 parallels malignant features.
Trisomy 3	3q (43.1% pRCC)	Occasionally associates with low-grade, and low-stage.
Gains	2 (20.7% pRCC) 16q (32 -55% pRCC), 12q (28 - 41.4% pRCC), 8q (19% pRCC), 3q (43.1% pRCC), 20q (32 -50% pRCC), loss of Y (87.2% pRCC) 5q (17.2% pRCC) 13 q (17.2% pRCC) 1 q (12.1% pRCC; 28% type 2 pRCC)	Duplication of 8q may be a useful marker of worse prognosis. *FBXO47* at 17q12 is often deleted.
LOH	6q (40% pRCC), 9p (36% PRCC), 1p (24% PRCC), 4q (36% pRCC), 13q (36% pRCC), 11q (15.5% pRCC; in 28% of type 2 pRCC), 3p (59%	LOH at *D9S171* (9q13) was associate with short survival. *RASSF1A* methylation in both type 1 and type 2.

	pRCC)	
	8p (12,1% PRCC; in 33% of type 2 pRCC)	In pRCC, LOH at 3p25–26 was more common than at 3p14.2 and the first was not associated with mutations of the *VHL* gene.
	Y (73% pRCC), Xp (28% PRCC); Xq (36% PRCC)	

Table 4 - Chromosomal abnormalities in papillary RCC. F-box protein 47 (FBXO47); Loss of heterozygosity (LOH); Ras-association (RalGDS/AF-6) domain family member 1 (RASSF1A); Papillary renal cell carcinoma (translocation-associated) (PRCC); Transcription factor binding to IGHM enhancer 3 (TFE3); pRCC (papillary RCC); von Hippel-Lindau tumor supressor (VHL) [15, 37, 60-77].

Gains of chromosomes 12, 16, and 20 are present in small papillary adenomas and the frequencies of gains of chromosomes 7, 17, 16, 12, 20, and loss of the Y chromosome are similar in both adenomas and carcinomas [35] (Table 4).

Papillary RCC with chromophilic cell type exhibit a set of chromosomal gains, characteristically including trisomies of chromosomes 7 and 17 [64]. Füzesi *et al.* reported three cases of pRCCs with clear cell cytomorphology showing loss of 3p but not trisomy of 17, and they concluded that pRCCs should be classified according to their cytomorphology rather than their growth pattern [15].

Microsatellite analysis of chromosome 9p suggests the existence of a yet unknown tumor suppressor gene centromeric to the *MTS* locus on 9p21, which may play a role in pRCC progression [78].

Gain of chromosomes 7p and 17p, loss of Y chromosome and additional gains (chromosome 3q, 8p, 12q, 16q and 20q) are frequently observed in type 1 pRCC, and chromosomal aberrations of type 2 pRCC show allelic imbalance of one or more of chromosomes 1p, 3p, 5, 6, 8, 9p, 10, 11, 15, 18 and 22: losses of chromosome 11 and 18 mainly, losses of 8 and losses from the short arm of chromosome 9 exclusively were reported. [15, 39, 76, 77, 79]. In gene profile studies, high-grade type 2 tumors have been differentiated from a mixed group of pRCC consisting of type 1 tumors, low-grade type 2 tumors, and tumors showing a mixed type 1 and low-grade type 2

morphology [38]. The considerable variation in the proportion of type 1 and 2 pRCC highlights the importance of assigning tumors into their correct subtype, according to established criteria [6].

Al-Saleem *et al.* reported a rare example of oncocytoma to pRCC progression with losses of chromosomes Y and 1, a common feature of oncocytoma, and a gain of chromosome 7, a feature of pRCC [80].

So far there are few reports of epigenetic alterations in pRCC. In one study of 61 tumors, *TU3A* (the candidate tumor suppressor gene – located at 3p21.1) was methylated in 42% of clear-cell RCC and 25% of pRCC [81, 82]. The *FHIT* gene encompasses the common fragile site *FRA3B* at 3p14, involved in purine metabolism. *FHIT* promoter methylation is common (52 to 53%) in both clear-cell RCC and pRCC [81]. *SPINT2* (serine peptidase inhibitor) which encodes a secreted inhibitor of c-MET activity (activating mutations in the *c-MET* proto-oncogene associate with familial pRCC, although somatic mutations are infrequent in sporadic pRCC) [81].

7. Treatment

Table 5 summarizes pRCC treatment.

Papillary RCC treatment
. Surgery Radical nephrectomy and lymph node dissection can cure early stage pRCC; relapses occur in 20–30% patients.
. Systemic therapy Renal tumors are highly resistant to both chemotherapy and radiotherapy. Sunitinib (tyrosine kinase inhibitor), sorafenib (tyrosine kinase inhibitor) and temsirolimus (mTOR inhibitor) approved by US Food and Drug Administration. Foretinib– tyrosine kinase inhibitor as well as of VEGR2 - ongoing Phase II clinical trial.

Table 5 – Papillary RCC treatment.Mammalian target of rapamycin (mTOR); Vascular endothelial growth factor receptor 2 (VEGFR2); pRCC (papillary RCC) [15, 29, 83-86].

Metastatic pRCC is characterized by resistance to systemic therapy and by poor survival [83]. The use of sunitinib and sorafenib, recently approved for advanced RCC, as well as other VEGF-based therapies warrant study in the clinical trials for patients with metastatic pRCC [83].

Prospective efforts to characterize the activity of sunitinib in metastatic pRCC yielded disappointing response rates [84]. A recent study of 41 patients with metastatic pRCC receiving sunitinib (13 patients) or sorafenib treatment (28 patients) reported a low overall partial response rate of 4.8% (2 of 41 patients) [85]. Both responders were treated with sunitinib and had response durations of 8 and 12 months [85]. The Advanced Renal Cell Carcinoma Sorafenib Expanded Access Program allowed patients in the United States and Canada with metastatic RCC to receive treatment with sorafenib prior to its regulatory approval [86]. This non-randomized, open-label program treated 158 with pRCC out of 1891 patients [86]. Of the 107 evaluable subjects with pRCC, 90 (84%) had a measurable response to treatment with 3 partial responders and 87 with stable disease for at least 8 weeks, while 17 (16%) patients developed early progression on treatment [86].

Treatment specific to the *c-MET* mutation associated with pRCC remains to be identified [83]. 17AAG, which acts by inhibiting heat shock protein and affects c-MET activation, achieved responses in a Phase II trial limited to pRCC patients [83]. Preclinical data, studying a monoclonal antibody to the c-MET ligand, hepatocyte growth factor, reported antitumor activity, which could offer a future novel treatment for patients with c-MET-dependent tumors [83].

Hereditary papillary renal tumor tends to be occult and, if not detected and treated, can spread to other organs [29]. Parenchymal sparing surgery (partial nephrectomy) is recommended when the largest renal tumor approaches 3 cm in size [29]. Patients whose tumors are < 3 cm are generally managed with observation [29]. The goal of management is to maintain the patient's renal function while minimizing the risk for metastasis [29].

Potential areas of systematic therapy for Hereditary Leiomyomatosis RCC will likely be designed to prevent increased HIF (Hypoxia induced factor) levels or target the transcription products of VHL-independent HIF accumulation, such as VEGF (Vascular endothelial growth factor) and TGF-α (Tumor growth factor alpha)/EGFR (Epidermal growth factor receptor) [16]. One attempt to block the downstream effectors of *FH* inactivation is through the use of erlotinib, an oral EGFR tyrosine kinase inhibitor (TKI) [16]. A multicenter phase II trial with this agent in patients with locally advanced and metastatic pRCC reported an overall RECIST (Response

evaluation criteria in solid tumors) response rate of 11% with an additional 24 patients (53%) experiencing stable disease [16]. Combination therapy with an mTOR inhibitor or VEGF pathway antagonist may potentiate the single agent activity of erlotinib [16]. A phase II trial of erlotinib (EGFR TKI) in combination with bevacizumab (monoclonal antibody against VEGF) is currently underway and is one of the trials designed to evaluate this strategy [16].

Rebecca Lim *et al*. reported a case of spontaneous regression of histologically confirmed metastatic type 2 pRCC in the absence of intervening systemic therapy or surgery [87].

8. Prognosis

Table 6 summarizes pRCC prognostic factors.

Predictors	
TNM staging system	The predictive value of the 2010 TNM regarding CSS of pRCC is not superior when compared to the 2002 TNM.
Nuclear grade	Significant differences for CSS of pT1b *vs.* pT2a and pT3b *vs.* pT3c in pRCC.
Histological subtype	Papillary histological subtype associates with good prognosis: low stage and grade, small tumor size and high % of CSS.
	Type 2 is usually larger, advanced and less differentiated and displays more frequently necrosis and lymphovascular invasion compare to type 1. Type 2 pRCC can present extensive nodal metastasis.
Tumor extension	The inferior vena cava, the renal vein, or its branches (stage T3b and T3c) occurs in 8.2%. Spread to mediastinal lymph nodes and supraclavicular lymph nodes are not unusual; such spread is considered to represent distant metastases and classified as M1 disease. Nodal involvement is not necessarily associated with worst prognosis. Visceral metastases in 5.7%–11%, including lung, bone and brain, and low median survival (9.1 months).
Tumor necrosis	Controversial parameter as negative predictor for metastasis-free and overall survival.
FN1	Increased FN1 mRNA expression seems to correlate to aggressive behavior.
EGF-R	Intermediate/strong EGF-R expression seems to associate to higher tumor grade, distant metastasis, and worst long-term survival.
Claudin-1	Loss of claudin-1 expression occurs in aggressive tumors and associates to shortened disease-specific survival

IMP3	IMP3 expression may predict tumor metastasis in patients with localized disease.
Chromosomal abnormalities	Losses of 8p, 9p, and 11q associate with higher T-stage and higher clinical stage, loss of 8p with positive M-stage, and loss of 9p and gain of 3q with positive N-stage. Polysomy 7 associates with higher nuclear grade and higher pathological stage.

Table 6 – Prognostic factors. Tumor-node-metastasis classification system (TNM); cancer-specific survival (CSS); Epidermal Growth Factor Receptor (EGF-R); Fibronectin (FN1); Insulin-like growth factor 2 mRNA binding protein 3 (IMP3); pRCC (papillary renal cell carcinoma). [2, 15, 44, 60, 88-97]

Two large pediatric series report the outcome of 32 patients with pRCC [9]. 75 % (24/32) presented with disease limited to the kidney, and 22 of the 24 were free of disease; death from disease occurred in one T2N0MX tumor and the other died from other causes [9]. Of the remaining eight patients with higher stage disease, three (T4N0MX, T3N1M0,T2,N2,M0) died of their disease [9].

Future Perspectives

Papillary RCC is the second most common renal cell carcinoma. Regrettably pRCC is usually asymptomatic or without specific symptoms and signs, and approximately 20% of pRCC are incidental findings. There are no specific tumor markers available for diagnostic, prognostic or predictive purposes. Papillary RCC diagnosis, prognosis and treatment are based on histopathologic features but their subtyping seems unsatisfactory. Molecular profiling is an emerging promising tool for new biomarker identification that may provide a better understanding of pRCC pathogenesis and eventually improve the accuracy of predicting prognosis and treatment of patients.

Executive Summary

Executive Summary
Epidemiology
Papillary RCC (pRCC) account for ~ 10% of renal cell tumors
pRCC is the most common histologic subtype in pediatric RCC
Range of age: third to eighth decades; male-to-female ratio: 2:1 to 3.9:1

Lifestyle Risk Factors Cigarette smoking and ACKD associate with pRCC, but not obesity; hypertension and fat or animal product intake remain controversial
Genetic syndromes Inhered pRCC: Hereditary papillary RCC (HPRCC); Hereditary leiomyomatosis RCC (HLRCC); PTEN hamartoma tumor syndrome (PTEN-HTS); Birt-Hogg-Dubé syndrome (BHD); Hyperparathyroidism-jaw tumor syndrome (HPTJT); Familial papillary thyroid cancer (FPTC)
Pathological features The morphologic classification of pRCC into type 1 and 2 tumors is supported by several studies but with limited molecular evidence to substantiate this subtyping
Immunohistochemical markers p504s (89.3 – 100%), rarely in other RCC; CK7 (90%: > 80% in type 1; 10-20% in type 2); MUC 1 and TOP2α with higher expression in type 1 pRCC; MYC in 67% of type 2 pRCC
Chromosomal abnormalities Main pRCC chromosomal abnormalities: trisomy 7, 17 and 3; others gains (2, 16q, 12q, 8q, 3q, 20q, 5q, 13q, 1q), loss of Y, LOH (6q, 9p, 1p, 4q, 13q, 11q, 3p, 8p, Y, Xp, Xq) Gain of chromosomes 7p and 17p, loss of Y chromosome and additional gains (chromosome 3q, 8p, 12q, 16q and 20q) frequent in type 1 pRCC; chromosomal aberrations of type 2 pRCC show allelic imbalance of one or more chromosomes: 1p, 3p, 5, 6, 8, 9p, 10, 11, 15, 18 and 22
Treatment Radical nephrectomy and lymph node dissection can cure early stage pRCC; relapses in 20–30% Highly resistant to both chemotherapy and radiotherapy; Sunitinib (tyrosine kinase inhibitor), sorafenib (tyrosine kinase inhibitor) and temsirolimus (mTOR inhibitor) approved by US Food and Drug Administration; Foretinib – tyrosine kinase inhibitor as well as of VEGR2 - ongoing Phase II clinical trial
Prognosis Specific prognosis features of pRCC remain controversial

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O meu sincero obrigada.

Future Medicine Author Guidelines

Contents

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- Additional reference sources for the interested reader

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Priority paper evaluations review significant, recently published original research articles carefully selected and assessed by specialists in the field (not a paper from the author's own group). The original research detailed in the chosen paper is discussed with the aim of keeping readers informed of the most promising discoveries/breakthroughs relevant to the subject of the journal through review and comment from experts.

Priority Paper Evaluations are intended to extend and expand on the information presented, putting it in context and explaining why it is of importance.

The ideal article will provide both a critical evaluation and the author's opinion on the quality and novelty of the information disclosed.

Word limit: 1500 words maximum (excluding summary, keywords and references).
Required sections (for a more detailed description of these sections see Article sections):

- Summary
- Keywords
- Summary of methods and results
- Discussion
- Future perspective
- Executive summary
- References: **Please note:** a maximum of 20 references are permitted
- Figures/tables: if necessary, only **one** of each is permitted
- Reference annotations
- Financial disclosure/Acknowledgements

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- Abstract/overview of meeting of approximately 100 words (120 words max)
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The author is challenged to include speculative viewpoint on how the field will have evolved 5–10 years from the point at which the article was written.

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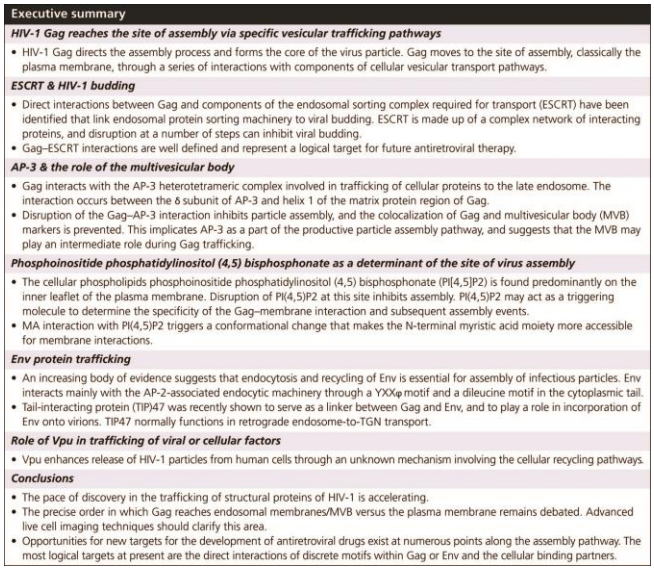

Executive summary

HIV-1 Gag reaches the site of assembly via specific vesicular trafficking pathways

- HIV-1 Gag directs the assembly process and forms the core of the virus particle. Gag moves to the site of assembly, classically the plasma membrane, through a series of interactions with components of cellular vesicular transport pathways.

ESCRT & HIV-1 budding

- Direct interactions between Gag and components of the endosomal sorting complex required for transport (ESCRT) have been identified that link endosomal protein sorting machinery to viral budding. ESCRT is made up of a complex network of interacting proteins, and disruption at a number of steps can inhibit viral budding.
- Gag–ESCRT interactions are well defined and represent a logical target for future antiretroviral therapy.

AP-3 & the role of the multivesicular body

- Gag interacts with the AP-3 heterotetrameric complex involved in trafficking of cellular proteins to the late endosome. The interaction occurs between the δ subunit of AP-3 and helix 1 of the matrix protein region of Gag.
- Disruption of the Gag–AP-3 interaction inhibits particle assembly, and the colocalization of Gag and multivesicular body (MVB) markers is prevented. This implicates AP-3 as a part of the productive particle assembly pathway, and suggests that the MVB may play an intermediate role during Gag trafficking.

Phosphoinositide phosphatidylinositol (4,5) bisphosphonate as a determinant of the site of virus assembly

- The cellular phospholipids phosphoinositide phosphatidylinositol (4,5) bisphosphonate (PI[4,5]P2) is found predominantly on the inner leaflet of the plasma membrane. Disruption of PI(4,5)P2 at this site inhibits assembly. PI(4,5)P2 may act as a triggering molecule to determine the specificity of the Gag–membrane interaction and subsequent assembly events.
- MA interaction with PI(4,5)P2 triggers a conformational change that makes the N-terminal myristic acid moiety more accessible for membrane interactions.

Env protein trafficking

- An increasing body of evidence suggests that endocytosis and recycling of Env is essential for assembly of infectious particles. Env interacts mainly with the AP-2-associated endocytic machinery through a YXXφ motif and a dileucine motif in the cytoplasmic tail.
- Tail-interacting protein (TIP)47 was recently shown to serve as a linker between Gag and Env, and to play a role in incorporation of Env onto virions. TIP47 normally functions in retrograde endosome-to-TGN transport.

Role of Vpu in trafficking of viral or cellular factors

- Vpu enhances release of HIV-1 particles from human cells through an unknown mechanism involving the cellular recycling pathways.

Conclusions

- The pace of discovery in the trafficking of structural proteins of HIV-1 is accelerating.
- The precise order in which Gag reaches endosomal membranes/MVB versus the plasma membrane remains debated. Advanced live cell imaging techniques should clarify this area.
- Opportunities for new targets for the development of antiretroviral drugs exist at numerous points along the assembly pathway. The most logical targets at present are the direct interactions of discrete motifs within Gag or Env and the cellular binding partners.

References

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Fantl JA, Cardozo L, McClish DK *et al*. Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis. *Obstet. Gynecol.* 83(1), 12–18 (1994).

Book example:

De Groat WC, Booth AM, Yoshimura N. Neurophysiology of micturition and its modification in animal models of human disease. In: *The Autonomic Nervous System (Volume 6)*. Andrews WR (Ed.), Harwood Academic Publishers, London, UK, 227–289 (1993).

Meeting abstract example:

Smith AB, Jones CD. Recent progress in the pharmacotherapy of diseases of the lower urinary tract. Presented at: *13th International Symposium on Medicinal Chemistry*. Atlanta, GA, USA, 28 November–2 December 1994.

Patent example:

Merck Frosst Canada, Inc. WO9714691 (1997).
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