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Renal Cell Carcinoma

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Abstract The global incidence of cases of kidney cancer has increased rapidly, and a relatively high incidence of kidney cancer has been reported in developed countries such as Northern and Eastern Europe. Various factors can affect the incidence and mortality of kidney cancer, including demographic risk factors, lifestyle factors, iatrogenic risk factors, nutritional factors and diet, occupation, and genetic factors. Renal cell carcinoma (RCC) refers to a tumor group with heterogeneity derived from renal tubular cells, which form almost all kidney cancer types. Clear cell RCC (ccRCC) is the most frequent renal tumor subtype, accounting for 75% of renal cancer, followed by papillar RCC(pRCC) making up approximately 10% of RCC. Hematoxylin-eosin staining shows a clear, eosinophilic cytoplasm in ccRCC cells. Epithelial cells forming the papillae and tubules have pRCC histological characteristics. Traditionally, genetic mutations of *VHL* and *MET* are the genetic features in ccRCC and pRCC, respectively. Recently, a new concept supports the contribution of mutations in some chromatin-modifier genes, including polybromo 1 (*PBRM1*), SET domain containing 2 (*SETD2*), BRCA1-associated protein-1 (*BAP1*), and lysine (K)-specific demethylase 5C (*KDM5C*). The metabolic disease concept in renal cancer is noted by researchers worldwide. The PD-1 pathway has been valued by researchers of kidney cancer in recent years, and new agents, such as anti-PD-1 monoclonal antibodies (nivolumab and pembrolizumab) and CTLA4 inhibitors (Ipilimumab), have been approved to treat advanced RCC. Partial nephrectomy (PN) and radical nephrectomy (RN) remain the standard management option for local RCC with a stage of T1 and T2, respectively. PN can also be selected for T2 stage RCC in suitable cases. Even though targeted therapy consisting of mainly the anti-VEGF and anti-mTOR pathways is recommended as the first-line and second-line treatment for RCC, the effectiveness and side effect of these therapies should be improved in future research.

Key words renal cell carcinoma, review, genetic mutation, management, immune checkpoint

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Introduction

The global total incidence of kidney cancer is increasing, probably due to global population growth[1]. A relatively high incidence of kidney cancer is found in developed countries, white individuals, and the male population. Clear cell renal cell carcinoma (ccRCC) makes up almost 75% of RCC pathology types, followed by papillary RCC (pRCC) and chromophobe RCC (chRCC)[2]. Genetic mutation is regarded to play a vital role in RCC. Traditionally, gene mutations in *VHL* and *MET* have been considered characteristic of ccRCC and pRCC, respectively[3, 4]. Mutations of a group of chromatin-remodeling genes, polybromo 1 (*PBRM1*), SET domain containing 2 (*SETD2*), BRCA1-associated protein-1 (*BAP1*), and lysine (K)-specific demethylase 5C (*KDM5C*), have been demonstrated to be associated with ccRCC[5]. Researchers have indicated that ccRCC is a disease of 3p loss due to the location of *VHL* and these chromatin remodeling genes on the same chromosome, 3p[6]. The concept of RCC as a metabolic disease has gradually formed a systematic theory[7]. Targeted therapy, such as anti-VEGF and anti-mTOR agents, were developed to treat advanced RCC based on these genetic mutation theories. Recently, immune check point proteins, such as PD-1/PD-L1 and CTLA-4, were found to play an important role in cancer immunity[8]. Relevant PD-1/PD-L1 and CTLA-4 inhibitors were developed to treat RCC. Surgery remains a standard management for RCC. Elective partial nephrectomy (PN), radical nephrectomy (RN) and focal therapy are, respectively, applied to treat local T1 stage RCC, T2 stage RCC and small mass tumors. However, these various basic theories of genetic mutation, a disease of 3p loss, metabolic disease and immune check points should continue to be investigated in the future to strengthen their interconnections.

Incidence, Mortality and Risk Factors

The global incidence of cases of kidney cancer were estimated to be 142,463 in 1990, with the number rapidly rising to 273,518 in 2008 and 294,501 in 2013[9, 10]. There was a mean global age-standardized incidence rate of 7.75 per 100,000 people per year in 1990. The number remained roughly stable with a mean of 4 in 2008 and 6.71 in 2013[9, 10]. The increase in the global incidence of cases of kidney cancer could be affected by population growth (35.0%) and the change in age structure (34.7%). Based on data collected from all confirmed cases of kidney cancer diagnosed from 2001 to 2010 in the U.S., the incidence of RCC in males is almost 2 times higher than in females[11]. Global age-standardized incidence rates per 100 000 kidney cancer case in males (mean 6.73) were also almost 2 times greater than in females (mean 2.97) in 2013[10]. There was positive correlation between age and incidence of kidney cancer. The elderly (age >75 yr) has the highest incidence of kidney cancer[12]. Black and white individuals have a relatively higher incidence rate of kidney cancer than yellow individuals in the USA[11]. The distribution of the incidence of kidney cancer shows significant differences worldwide. There is a relatively high incidence of kidney cancer distributed in Northern and Eastern Europe, North America, and Australia, and a relatively low incidence is estimated in much of Africa and South-East Asia[10, 13, 14]. Interestingly, black people in Africa have a lower incidence of kidney cancer than black people in the USA. The incidence rate of kidney cancer in developed countries is much higher than in developing countries. The age-standardized incidence rates per 100,000 cases of kidney cancer in both females and males in developing countries is 1.34, and the number rises to 3.27 in developed countries. An increase of 35.8% in the incidence of kidney cancer was reported in both males and females in developed countries from 1990 to 2013. Similarly, an increase of 34.32% was reported in developing countries[10].

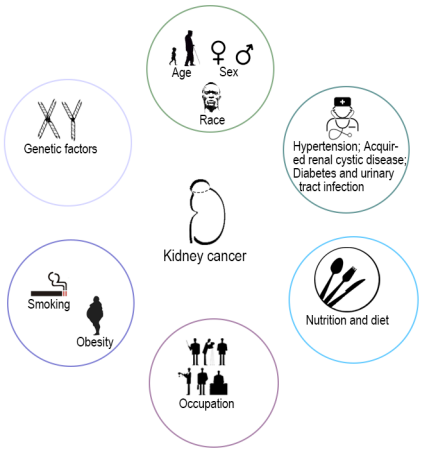

Figure 1. Kidney cancer risk factors.

There was no obvious change in mortality due to kidney cancer from 1990 to 2013. Global deaths caused by kidney cancer were 77,900, and the age-standardized death rate of kidney cancer was 2.1 in 1990. The global death rate caused by kidney cancer was 134,000 and the age-standardized death rate 2.2 in 2013[15]. There was a significant difference in kidney cancer mortality rates between developed and developing countries. The age-standardized death rate in developed countries was 3.7 while it was 1.3 in developing countries in 2013[16]. Additionally, both numbers were 2.8 vs. 1.3 in 2012[1]. In 2012, Lithuania, the Czech Republic, Latvia and Estonia were reported to have the highest mortality rates, and Micronesia/Polynesia, Middle Africa, Western Africa and South-Central Asia had the lowest death rates due to kidney cancer[1]. Similar to the incidence of kidney cancer, the mortality rate was also affected by sex. The male mortality rate reached up to threefold greater than that of the female rate according to an analysis of global data (2003-2007)[12].

Various risk factors can affect the incidence and mortality of kidney cancer, such as demographic risk factors (race, age, and sex), lifestyle factors (smoking and obesity), iatrogenic risk factors (hypertension and use of antihypertensive medications, acquired renal cystic disease, diabetes and urinary tract infection), nutritional factors and diet, occupation, and genetic factors (**Figure 1**)[17, 18]. As described above, the distributional difference in the incidence and mortality of kidney cancer directly reflects that race, age and sex have an influence on kidney cancer prevalence. Tobacco continues to be the dominant risk factor in global male kidney cancer deaths, while it is weakly associated with kidney cancer in females. Instead of smoking, obesity is a stronger risk factor for kidney cancer in females than males. A meta-analysis by Callahan et al. showed that obesity (BMI $\geq$ 30 kg/m2) was associated with ccRCC and chRCC but not with pRCC[19]. Numerous studies have suggested that blood pressure is associated with kidney cancer risk[20, 21]. Recently, a meta-analysis by Khemayanto et al. reported a positive association between hypertension and kidney cancer, and a dose-response analysis revealed that each 10 mmHg increase in systolic blood pressure and diastolic blood pressure were significantly associated with a 10% and 22% increased risk of kidney cancer, respectively[22]. Acquired renal cystic disease is a definite risk factor for RCC, and the period of dialysis may be related to the higher incidence of RCC[23, 24]. Other diseases, including diabetes and urinary tract infection, have also been reported as potential risk factors for RCC, but the conclusions have been controversial[25-27]. A large number of studies involved total fat or various types of

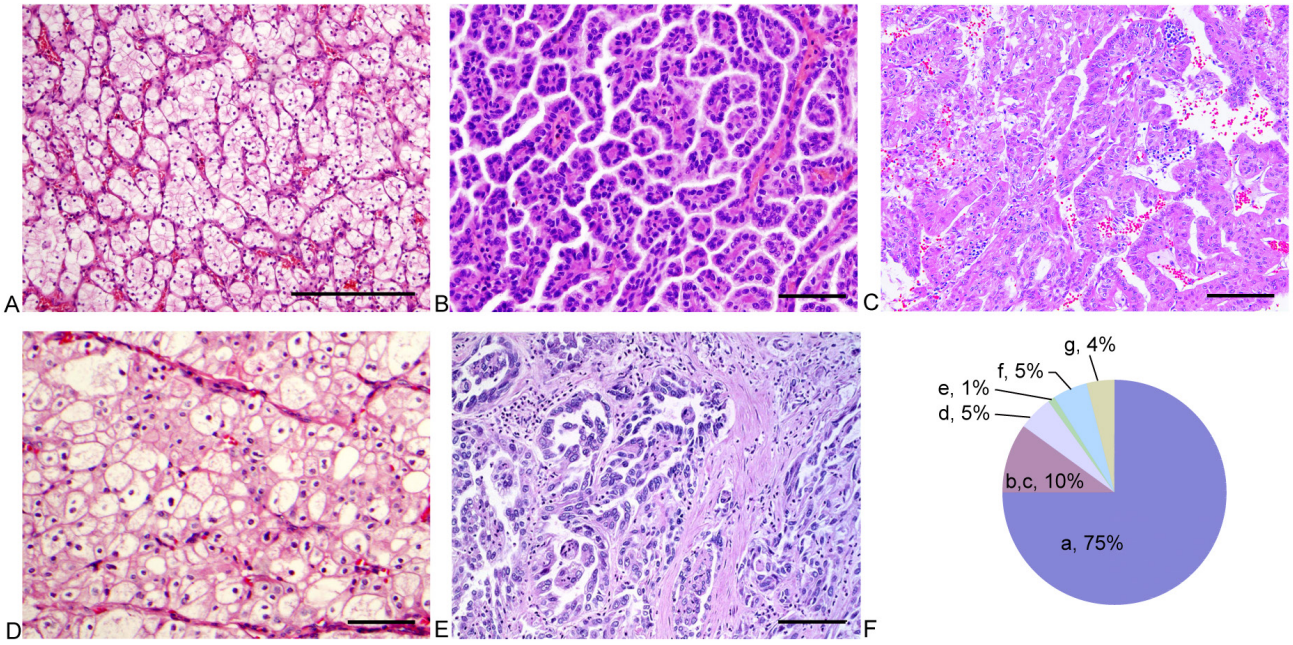

Figure 2. Pathological features for several main pathology types of renal cell carcinoma(RCC). A: clear cell renal cell carcinoma(ccRCC), low grade ccRCC with thin sinusoidal vessels and alveolar growth pattern; B: Type 1 papillary RCC, papillary RCC with a low grade nuclei, scanty cytoplasm and a single raw of tumor cells lining papillae; C: Type 2 papillary RCC, papillary RCC with a high grade nuclei, abundant eosinophilic cytoplasm and stratified/pseudostratified tumor cells lining papillae; D: Chromophobe RCC(chRCC), this tumor is characterized by distinct cell membrane, reisinoid nuclei and perinuclear clearing; E: Collecting duct carcinoma, this tumor shows tubular or tubulopapillary carcinoma with infiltrative growth, high nuclear grade and desmoplatic stroma; F: Pie chart for occurrence rate of several main pathology types of RCC(a: ccRCC; b: Type 1 papillary RCC; c: Type 2 papillary RCC; d: chRCC; e: Collecting duct carcinoma; f: Unclassified RCC; g: Other rare renal tumour). Scale bar = 100um.

fat intake and RCC risk, and their results were inconsistent[28]. Meta-analyses showed that alcohol and fruit and vegetable intake can reduce the risk of kidney cancer[29, 30]. Although RCC is not a typical occupational disease, exposure to some organic compounds, such as trichloroethylene (TCE), can be linked to kidney cancer[31]. A review did not support that occupational exposure to TCE is a risk factor for cancer of any specific site[32]. A corresponding familial syndrome in each of the common histologic subtypes of RCC was caused by a distinct genetic alteration, even though these syndromes are relatively rare[33]. Various gene mutations are associated with RCC, and two typical genetic variations in *VHL* and *MET* are involved in occurrence of ccRCC and pRCC, respectively[34, 35]. The specific content of the kidney oncology gene and histologic subtypes will be discussed in subsequent sections of the article.

Pathological classification of RCC

RCC refers to a heterogenous tumor group derived from renal tubular cells[36]. According to the morphological and genetic characteristics of RCC described by WHO, there are more than a dozen RCC subtypes[37, 38]. ccRCC, pRCC and chRCC are the three most common types of RCC and consist of approximately 90% RCCs. According to the 2016 WHO classification of kidney tumors, 16 renal cell tumors were classified and five renal tumor entities were newly identified, including hereditary leiomyomatosis and RCC syndrome-associated RCC, succinate dehydrogenase-deficient RCC, tubulocystic RCC, acquired cystic disease-associated RCC and clear cell papillary RCC[38]. Most subtypes of RCC classified by WHO in 2016 are presented in **Table 1**[38-40]. Here we emphatically introduce several common types of RCC classified by WHO.

Clear cell renal cell carcinoma (ccRCC)

Clear cell RCC generally consists of solitary cortical neoplasms it occurs equally in either kidney. It is the most frequent renal tumor subtype, making up to 75% of RCCs, and it exhibits a typical golden yellow tumor surface due to the abundant lipid content of the cells (**Figure 2A, F**). Hematoxylin-eosin staining shows solid alveolar or acinar pattern of tumor cells with a regular network of thin walled sinusoidal blood vessels(**Figure 2A**).The tumor cells have a round nucleus with evenly distributed chromatin and variablesized nucleolus depending on the tumor grade, and havea clear oreosinophilic cytoplasm[2]. Von Hippel-Lindau (VHL) disease will result in this tumor type, which is a hereditary RCC. The alterations in chromosome regions (-3p,+5q22, -6q, -8p, -9p, -14) are identified as its genetic features[37]. PAX-8 with nuclear staining and CA9 with membranous staining are regarded as useful markers based on immunohistochemical methods[41].

Papillar renal cell carcinoma (pRCC)

pRCC makes up approximately 10% of RCCs, second to ccRCC (**Figure 2F**)[42-44]. Bilateral and multifocal tumors occur more frequently in pRCC than in other renal malignancies. The tumor tissue, which is usually friable, is bounded by a thick pseudocapsule and frequently shows fibrosis and hemorrhage. Epithelial cells forming the papillae and tubules are its histological characteristics. Two distinct groups, type 1 and type 2, are defined in pRCC. In type 1, papillae are covered by a single raw of low nuclear grade tumor cells(nuclear grade 1 or 2) with scanty cytoplasm(**Figure 2B**). Type 2 shows a higher nuclear grade(nuclear grade 3 or 4) with abundant eosinophilic cytoplasm and stratified or pseudostratified nuclei(**Figure 2C**)[2]. Hereditary papillary RCC will result in type 1 pRCC with mutation of

Table 1. Classifiation of rell cell carcinoma by WTO in 2016

RCC subtype	Incidence(%)	Genetic	Histological characteristics	Gross appearance	Metastasis and Prognosis
Clear cell RCC	75	-3p,+5q22,-6q, -8p,-9p,-14	Clear cytoplasm due to abundant lipid content of the cells; cells with eosinophilic cytoplasm	Solitary,rare multicentric or bilatera; typically golden yellow(necrosis, cystic degeneration, hemorrhage, calcification, ossification, extension into the renal vein and sarcomatoid change may occur)	Aggressiveness according to grade, stage and sarcomatoid chang; most commonly metastasize hematogeneously via the vena cava primarily to the lung
Papillar RCC	10	+3q,+7,+8,+12, +16,+17,+20,-Y	Papillae and tubules formed by epithelial cells;macrophages; psammoma bodies; type 1(papillae covered by small cells with scanty cytoplasm) or type 2 (higher nuclear grade with eosinophilic cytoplasm and pseudostratified nuclei)	Multicentric, bilateral or solitary; frequently contain necrosis,sarcomatoid differentiation	Aggressiveness according to grade, stage and sarcomatoid chang
Chromophobe RCC	5	-1, -2, -6, -10, -17, -21, hypodiploidy	Large polygonal cells with reticulated cytoplasm and prominent cell membranes; irregular and multinucleated cells	Solitary; homogeneously gray or gray-brown	10% mortality,distant metastasis into lung, liver(more frequently) and pancreas
Collecting duct carcinoma	1	-1q, -6p,-8p, -13q, -21q, -3p (rare)	A tubulo-papillary architecture with a characteristic desmoplastic stroma reaction	Solitary; located in the central region of the kidney and have a gray-white appearance with irregular borders	Extremely aggressive with frequent metastasis to regional lymph nodes, lung, liver, bone and adrenal glands
Renal medullary carcinoma	Rare	Unknown	Moderate to abundant eosinophilic cytoplasm with a hyperchromatic large nucleus containing a prominent nucleolus	Solitary; white, gray white, or tan white in color, firm, and infiltrative, with foci of necrosis	Metastases especially to the lung and bone; time from diagnosis to death averaged 3 months
Xp11 translocation carcinoma	Rare	t (X; 1) (p11.2; q21), t (X; 17) (p11.2; q25), Other	Papillary architecture comprised of clear cells with voluminous clear to eosinophilic cytoplasm	Solitary; unencapsulatedandis yellow, tan,and soft	Poor prognosis, presenting at advanced stages, frequently with lymph node metastasis at diagnosis
Multilocular cystic renal neoplasm of low malignant potential	Rare	*VHL* gene mutations	Clear cytoplasm, small dark nucle	Solitary, rare bilateral; complete cystic appearance without a solid tumoral component	No metastases
Succinate dehydrogenase-deficent renal carcinoma	Rare	*SDH* gene mutation	Clear cells or eosinophilic cells, cytoplasmic vacuoles	Solid brown, sometimes more red tumor,Cystic changes	Most of prognosis is good, case of sarcomatoid differentiation is less favorable

Table 1. Classifiation of rell cell carcinoma by WTO in 2016(Continued)

RCC subtype	Incidence(%)	Genetic	Histological characteristics	Gross appearance	Metastasis and Prognosis
Mucinous tubular and spindle cell carcinoma	Rare	-1, -4, -6, -8, -13, -14, +7,+11,+16, +17	Low-grade renal epithelial neoplasms with tubular and spindle cell features and mucinous stroma	Solitary; the cutsurfaceis yellow to tan brown,and the tumor is firm	Favorable prognosis and regional lymph nodes metastases
Tubulocystic RCC	Rare	+17,+7	Cysts are lined by hobnail-like or big cells with huge nucleoli whose cytoplasm is eosinophilic and abundant	A multiple cystic sponge like aspect,and thin walls without vegetations	Only 4 of 70 reported cases showed metastasis to bone, liver, and lymph nodes
Acquired cystic disease-associated RCC	Rare	+1,+2,+3,+6,+7,+16, +17,+Y	The tumors are either solid or cystic or both and of papillary architecture	Most tumors were well-circumscribed, larger tumors with a thick fibrouscapsule;the smaller ones were illdefined and irregular, which were filled with necrosis, coagulated blood, or transparent liquid	Most tumours have indolent behaviour
Clear cell papillary RCC	Rare	-3p,+7,*VHL*,*A358G, R120G* mutations	Low-grade clear epithelial cells arranged in tubules and papillae with a predominantly linear nuclear alignment away from the basement membrane	Tan-white to yellow in color, well circumscribed, and well encapsulated	Indolent behaviour
RCC, unclassified	<5	Unknown	Sarcomatoid morphology without recognizable epithelial elements, mucin production or unrecognizable cell types	Solitary; and the cut surface appeared grayish-red, with parts showing necrotic bleeding, resembling rotten fish specimens	Highly aggressive biological behavior and poor clinical outcome
Papillary adenoma	Rare	Unknown	A tubulo-papillary architecture similar to cellular types 1 and 2 in papillar RCC	Solitary;well circumscribed, greyish or white lesion	Do not metastasize but should be cautious
Oncocytoma	Rare	Unknown	Densely granular eosinophilic cytoplasm and round and regular nuclei	Circumscribed, non-encapsulated, mahoganybrown or pale yellow with a central stellate scar	Benign tumor

VHL, von Hippel–Lindau disease tumor suppressor; SDH, succinate dehydrogenase; RCC, renal cell carcinoma.

Table 2. Hereditary renal cell tumors

Syndrome	Chromosome	Gene	Renal tumor	Other organ manifestations
Von Hippel-Lindau	3p25-26	*VHL*	Clear-cell RCC	CNS haemangioblastomas; pheochromocytoma; retinal angiomas; pancreatic endocrine tumours; paragangliomas; cystadenomas of broad ligament or epididymis
Hereditary papillary RCC	7q31-34	*c-MET*	Type 1 papillary RCC	-
Hereditary leiomyomatosis and renal cell cancer syndromes	1q42-43	*Fumarate hydratase*	Type 2 papillary RCC	Leiomyomas of skin or uterus; uterine leiomyosarcomas
Hyperparathyreoidism-jaw tumor syndrome	1q25	*HRPT2*	Epithelial-stromal mixed tumors, papillary RCC	Tumors of the parathyroidea; fibro-osseous jaw tumors
Birt-Hogg-Dubé syndrome	17p11	*BHD*	Multiple chromophobe RCC, oncocytoma, papillary RCC	Facial fibrofolliculoma; pulmonal cysts; spontaneous pneumothorax
Tuberous Sclerosis	9q34 or 16p13	*TSC1* or *TSC2*	Multiple, bilateral angiomyolipomas, lymphangioleiomyo-matosis; rare clear cell RCC	Cardiac rhabdomyomas; neurological disorders or seizures; multiple skin findings, including angiofibromas, fibromas, and nevi
Constitutional translocation chr.3	3p13-14	-	Multiple, bilateral clear cell RCC	-
Familiary papillary thyroid carcinoma	1q21	-	Papillary RCC oncocytomas	Papillary thyroid carcinoma

RCC, renal cell carcinoma; CNS, central nerous system; TSC, Tuberous Sclerosis; MET, hepatocyte growth factor receptor; BHD, Birt-Hogg-Dubé; HRPT, hyperparathyroidism.

the *c-MET* gene and hereditary leiomyomatosis, and renal cell cancer syndromes (HLRCC) with mutation of the fumarate hydratase gene are associated with type 2 pRCC. The alteration in chromosome regions (+3q,+7,+8,+12,+16,+17,+20, -Y) has been identified as the genetic features[37].

Chromophobe renal cell carcinoma (chRCC)

ChRCC accounts for approximately 5% of RCC (**Figure 2F**)[45]. Solitary tumors commonly occur with a homogeneous gray or gray-brown gross appearance. Compared with ccRCC and pRCC, this type of RCC has a better prognosis and a mortality less than 10%[45]. These tumors consist of large polygonal cells with a reticulated cytoplasm and prominent cell membranes, reisinoid wrinkled nuclei and perinuclear claring (**Figure 2D**). They must be differentiated from those of oncocytoma due to the eosinophilic variation among the two types of renal cancer. Birt-Hogg-Dubé (BHD) syndrome is related to chRCC with mutation of the *BHD* gene[2]. The alteration of chromosome regions (-1, -2, -6, -10, -17, -21, hypodiploidy) has been identified as its genetic feature[37].

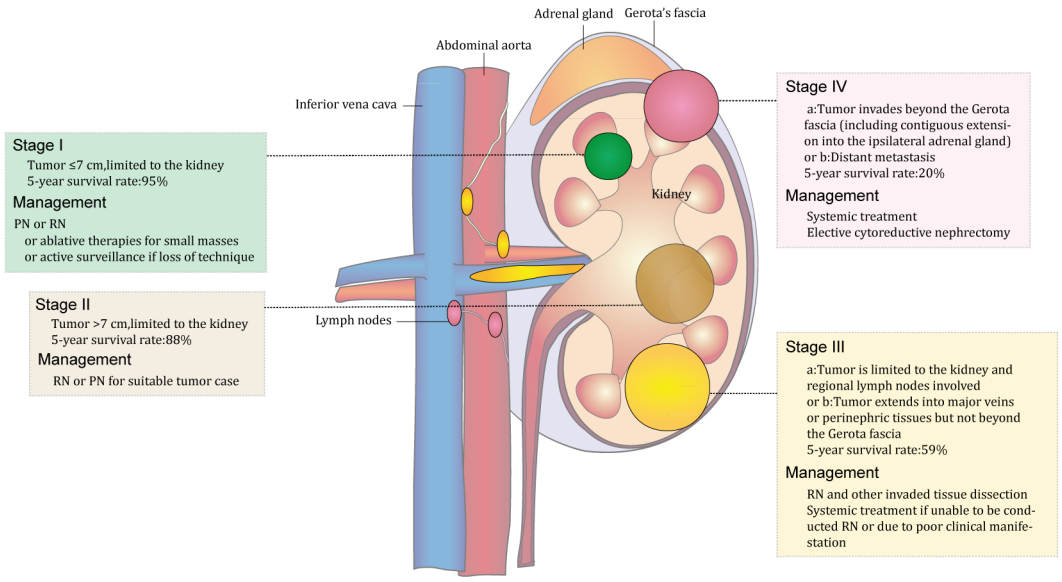

Figure 3. Schematic diagram of the stages of kidney cancer and relevant recommended treatment options.

Collecting duct carcinoma

This is an extremely aggressive renal tumor type accounting for <1% of all renal cancer types. It usually occurs in the central region of the kidney and exhibits a firm, gray-white appearance with irregular borders. Histologically, it has a tubulo-papillary architecture with a high nuclear grade and a characteristic desmoplastic stromal reaction(**Figure 2E**)[2]. The alteration of chromosome regions (-1q, -6p, -8p, -13q, -21q, -3p) has been identified as its genetic feature[37].

Hereditary renal cell carcinoma

There were two routes of renal cancer occurrence: a sporadic form and a hereditary form[46]. Over the years, numerous hereditary tumor syndromes with a tendency toward the development of RCC have been identified. Some mutant genes have been detected among patients with hereditary tumor syndromes, according to molecular analysis of their renal tumor tissues, such as the association of *VHL*, *MET*, *FH*, *BHD* and *HRPT2* genes mutation with Von Hippel-Lindau disease, hereditary papillary RCC, hereditary leiomyomatosis and renal cell cancer syndromes (HLRCC), Birt-Hogg-Dubé (BHD) syndrome, and hyperparathyroidism-jaw tumor (HPT-JT) syndrome. These hereditary disease have been associated with various renal tumor pathological types. VHL disease, the most frequent familial renal cancer syndrome, is associated with ccRCC and with *VHL* wild type gene loss[47]. Hereditary papillary RCC syndrome and hereditary leiomyomatosis and renal cell cancer syndromes (HLRCC) are, respectively, associated with histological type 1 pRCC and type 2 pRCC[48, 49]. An activating mutation of the *MET* proto-oncogene and loss-of-function mutation in *FH* in the germ line are both respective features in patients. Renal tumors are one feature of these hereditary renal cancer symptoms, and there are many extrarenal organ manifestations, such as central nervous system (CNS) hemangioblastomas, pheochromocytoma and retinal angiomas, which also occur in patients with familial renal cancer syndrome together with renal tumors. Other hereditary renal cancer symptoms are summarized in **Table 2**[2].

Prognostic factors and staging systems for RCC

Various prognostic factors and models have been developed to evaluate the prognosis of RCC[50-53]. Thus far, a large amount of prognostic factors, including TNM stage, tumor factors, nuclear grade, histological type and clinical factors, have been discussed[54]. Although the accuracy of currently developed prognostic factors and staging systems remain controversial, the TNM system developed and maintained by the American Joint Committee on Cancer (AJCC) and the International Union Against

Table 3. TNM staging system for kidney cancer

Primary tumor(T)				Regional lymph nodes (N)		Distant metastasis (M)	
Tx	Primary tumor is unable to be evaluated			Nx	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No primary-tumor evidence			N0	No regional lymph node metastasis	M1	Distant metastasis
T1	Tumor ⩽ 7 cm,limited to the kidney	T1a	Tumor ⩽ 4 cm	N1	Metastasis in a single regional lymph node(s)		
		T1b	Tumor >4 cm				
T2	Tumor >7 cm, limited to the kidney	T2a	Tumor ⩽ 10 cm				
		T2b	Tumor >10 cm				
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia	T3a	Tumor extends into the renal vein or its segmental (segmental vein) branches, or invasion of pelvicaliceal system or tumor invades perirenal and/or renal sinus fat but not beyond the Gerota fascia				
		T3b	Tumor grossly extends into the vena cava below the diaphragm				
		T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava				
T4	Tumor invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)						

Cancer (UICC) has been referred to extensively to evaluate the prognosis of renal cancer[55-57]. Like the abbreviation of the name in the TNM system, three key prognostic factors are associated with renal cancer: local extension of the primary tumor (T), involvement of regional lymph nodes (N), and presence of distant metastases (M). The current TNM system represents the eighth edition, and details of the edition are shown in **Table 3**[57, 58].

Modification of this system has continued since the establishment of the TNM system in 1978[59]. The major revision focuses on the local extension of the primary tumor (T). Various cut points (4.0, 4.5, 5.5 and 6.5 cm) have been established, even to explore the best cut point showing a significant difference in the prognosis of renal cancer. The cut point was defined as 2.5 cm in the 1978 edition of the TNM system, while the T2 category was expanded into four subcategories (T2a: >2.5-5 cm; T2b: >5-7.5 cm; T2c: >7.5-10 cm; T2d: >10 cm) in the 1993 revised edition by AJCC. The current recommended 7 cm T1/T2 cut point was established in 1997[60]. The current recommended 4 cm pT1a/pT1b cut point (reference value for partial nephrectomy) was established in 2002 according to the research results[61-63].

As evidence to define T3 and T4, it has been reported that renal tumors extending to perirenal fat, ipsilateral adrenal gland, renal sinus fat, kidney capsular and vena cava and renal vein thrombosis are associated with a worse prognosis, even if these conclusions remain controversial. Roberts et al. found that patients with pT1 RCC and pT3a RCC have the same recurrence-free survival rate[64]. Jeon et al. found that perirenal fat invasion has prognostic significance in patients with a tumor greater than 7 cm but less than or equal to 7 cm[65]. Adrenal gland involvement was noted in the TNM system in 1987. Initially, adrenal gland invasion or invasion into perirenal tissues (not beyond the Gerota fascia) was defined as T3a, and then it was defined as T4 due to the ipsilateral adrenal invasion with the same worse prognosis compared with tumor infiltration beyond the Gerota fascia[66, 67]. The renal sinus contains lymphatics and numerous large thin-walled tributaries of the main renal vein, and there is no fibrous capsule between the cortical tissue and the sinus, enabling RCC to gain access to the vein more readily than through the fibrous renal capsule[68]. The current TNM system regards renal sinus invasion as an important prognostic parameter in renal staging despite a few argumentative reports[69, 70]. Capsular invasion is more likely to be an independent prognostic factor in high size or grade tumors, but results have been inconsistent concerning the localization of T1 and T2 renal cancer[67, 71, 72]. Klaver et al. demonstrated that different levels of subdiaphragmatic tumor thrombus have significantly different cancer-specific survival, and they suggested a need to reclassify T3 of the 2002 version of the TNM system[73]. A retrospectively review of 1122 patients reported that patients with renal vein involvement have a 5-year survival rate of 43.2%; 37% have inferior vena cava (IVC) involvement below the diaphragm and 22% have caval involvement above the diaphragm[74]. Nevertheless, some studies have not found a significant difference in the survival rate between renal vein involvement and IVC invasion[75, 76]. The current version of the TNM system supports that renal vein, IVC involvement below the diaphragm and IVC involvement above the diaphragm should be classified as three different prognosis grades.

Regional lymph node involvement and distant metastasis have been demonstrated to be independent prognostic factors for a worse prognosis in the patients with renal cancer[77], providing evidence to define T3 and T4 in the current TNM system. In the 2002 TNM system, two grading levels for lymph nodes were distinguished: patients with one affected lymph node (N1) and those with multiple affected nodes (N2). The prognosis between N1 and N2 was controversial[78]. Terrone et al. demonstrated no statistically significant difference between pN1 and pN2 and supported that the involvement of 4 lymph nodes could be significantly differentiated from N1[56]. The clinical data clearly showed that distant metastasis had independent prognostic value and that bone or liver metastases were related to lung metastases in particular[79].

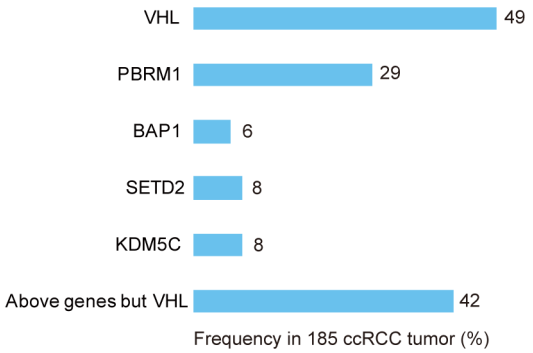

Figure 4. Mutation case frequency of *VHL* and chromatin-modifier genes (*PBRM1*, *BAP1*, *SETD2*, and *KDM5C*) in 185 ccRCC cases.

In addition, histological necrosis and microvascular tumor invasion[80, 81] were demonstrated to be independent prognostic factors for RCC. Fuhraman system has been frequently applied to grade RCC, but some studies show that the grading system is not suitable to grade chRCC and pRCC[82, 83]. **Figure 3** evocatively shows the TNM stage of RCC and its relative management options.

Genetic alterations in ccRCC

It has been reported that various genetic mutations contribute to RCC. Two main types of genetic mutations have been associated with ccRCC: mutation of the *VHL* gene and of some chromatin-modifier genes, including polybromo 1 (*PBRM1*), SET domain containing 2 (*SETD2*), BRCA1-associated protein-1 (*BAP1*), and lysine (K)-specific demethylase 5C (*KDM5C*)[84, 85]. The genetic alteration of *Met* is known to be related to pRCC. Nevertheless, not all cases of RCC exhibit these genetic alterations, and there are detectable rates of *VHL* or *PBRM1* in ccRCC pathological specimens. Hakimi et al. found that the frequency of overall genetic mutation was 65% and *VHL* gene mutation was 49.2% in 185 ccRCC samples. They also reported that the alternation frequency rate of the chromatin-modifier genes *PBRM1*, *BAP1*, *SETD2*, and *KDM5C* in their 185 ccRCC samples was 29.2%, 5.9%, 7.6% and 7.6%, respectively[5]. The alteration frequency with one chromatin-modifier gene was 42% in ccRCC samples (**Figure 4**). Since its discovery, *VHL* has been deemed to be a very important genetic mutation that is significantly associated with ccRCC[4]. In fact, most patients with von Hippel–Lindau disease (a hereditary cancer syndrome) carry the mutation gene locus in the 25 subarea of the short arm of chromosome 3, with a high risk of renal cysts and clear cell kidney cancer. *VHL* gene inactivation in the renal epithelium can initiate ccRCC. VHL protein is a complex consisting of elongin B, elongin C, and cullin 2, and it functions to target hypoxia-inducible factors (HIFs) for ubiquitin-mediated degradation. Patients with von Hippel–Lindau disease inherit only one functional copy of the *VHL* gene and undergo a subsequent loss of heterozygosity (LOH)[86]. Loss of *VHL* normal function in the translation of VHL proteins will result in an accumulation of HIFs due to a loss of function in targeting HIFs for ubiquitin-mediated degradation. It has been demonstrated that the VHL protein complex functions in ubiquitin-mediated HIF degradation

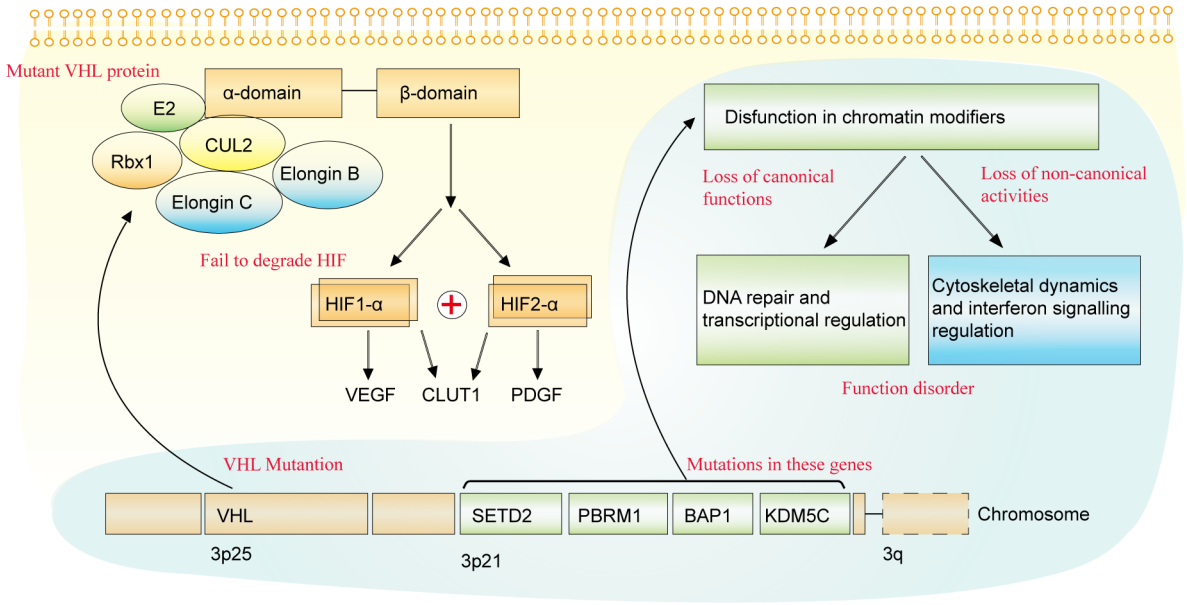

Figure 5. The genetic basis of ccRCC with *VHL* (located on 3p35) and chromatin-modifier gene (*PBRM1*, *BAP1*, *SETD2*, and *KDM5C*, mainly located on 3p21) mutations. *VHL* mutation: VHL protein is a complex consisting of elongin B, elongin C, and cullin 2 and functions to target HIFs for its ubiquitin-mediated degradation. *VHL* mutation and hypoxia exposure of VHL protein will result in a failure of HIFs to undergo ubiquitin-mediated degradation and accumulation. HIF1-α or HIF2-α with HIF-β can bind to HIF response element (HER) in the cell nucleus to increase mRNA levels coding for VEGF, PDGF, and CLUT1, among others. Chromatin-modifier gene mutation: Chromatin-modifiers have two main functions in ccRCC, including canonical functions and noncanonical functions. The former are involved in DNA repair and transcriptional regulation and the latter in the regulation of cytoskeletal dynamics and interferon signaling. Chromatin-modifier gene (*PBRM1*, *BAP1*, *SETD2*, and *KDM5C*) mutations and loss of their proteins will affect the above two main functions in ccRCC. ccRCC, clear cell renal cell carcinoma; VHL, von Hippel–Lindau disease tumor suppressor; HIF, hypoxia-inducible factors; VEGF, vessel endothelial cell growth factors; GLUT1, glucose transporter type 1; PDGF, platelet derived growth factor; +, Positive Activation.

under normoxia conditions[86]. Because a proline residue of HIF-α must undergo hydroxylation for it to bind VHL protein[87, 88], the extent of hydroxylation depends on oxygen tension due to the gradual process of proline hydroxylases acting on HIF-α[89]. In addition, hydroxylation of an asparagine residue of the HIF-α amino acid sequence can also block its interaction with the transcriptional coactivator p300[90]. The VHL complex fails to target HIFs for ubiquitin-mediated degradation, resulting in an accumulation of HIFs under hypoxia conditions. As transcription factors, HIFs consist of one HIF-α subunit (HIF1α, HIF2α, or HIF3α) and a member of the HIFβ family[89, 91]. HIF1-α or HIF2-α with HIF-β can bind to HIF response element (HER) in the cell nucleus to increase the mRNA levels of genes coding for vessel endothelial cell growth factors(VEGF), platelet derived growth factor(PDGFB), platelet derived growth factor 1(GLUT-1), transforming growth factor apha (TGF-α), erythropoietin, atypical protein kinase C and extracellular matrix protein, among others. The activating HIFs have effects on the angiogenesis, glycolysis and metastasis of cancer cells[34, 92]. Overall, the above two factors influence *VHL* gene loss mutations, and exposure of the VHL protein to hypoxia will result in a failure of HIFs to undergo ubiquitin-mediated degradation and thus their accumulation (**Figure 5**).

Recent studies have focused on several novel recurrent mutations in chromatin remodeling genes, mainly *PBRM1*, *SETD2*, *BAP1*, *KDM5C*, *KDM6A* and *MLL2*[5, 84, 93-98]. These genes encode histone-modifying enzymes. *SETD2*, *KDM5C*, *KMT2D* and *KDM6A* were first identified in 2010, and *PBRM1* and *BAP1* were reported subsequently[84, 93]. Histone-lysine N-methyltransferase SETD2 (SETD2) is a histone H3 lysine 36 methyltransferase. Lysine-specific demethylase 5C (KDM5C) is a histone H3 lysine 4 demethylase. Histone lysine N- methyltransferase 2D (KMT2D namely, MLL2) is a histone H3 lysine 4 methyltransferase. Lysine-specific demethylase 6A (KDM6A) is a histone H3 lysine 27 demethylase [84]. Ubiquitin carboxyl-terminal hydrolase BAP1 (BAP1) is a deubiquitinase that targets the monoubiquitylation of lysine 119 on histone H2A[99]. Polybromo1 (PBRM1) is a component of the switch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complex, which is involved in nucleosome repositioning[85]. DNA in eukaryotic cells that are not dividing is assembled around core histones (H2A,H2B,H3 and H4 family proteins) named the nucleosome. The nucleosome along with other protein complexes form a complex macromolecule called chromatin[100]. DNA transcription must be regulated by a series of actions of chromatin remodeling factors aided by a complex coding system of posttranslational modifications of the nucleosome within chromatin. The post-translational modifications include methylation, acetylation, phosphorylation, ubiquitylation, sumoylation, citrullination, and ADP ribosylation. Four types of chromatin remodelers have been identified, including SWI/SNF, imitation switch (ISWI), chromodomain helicase DNA-binding (CHD), and DNA helicase INO80[101]. PBRM1, BAP1, SETD2, KDM5C and KDM6A have been reported to play important roles in posttranslational modification within chromatin. Thus, mutation of these genes and loss of these proteins will affect chromatin remodeling and DNA transcription. In general, chromatin-modifiers have two main functions in RCC, including canonical functions and noncanonical functions; the former is involved in DNA repair and transcriptional regulation, and the latter plays a role in the regulation of cytoskeletal dynamics and interferon signaling (**Figure 5**)[102]. It has been suggested that the loss of function of chromatin-modifiers, including *PBRM1*, *BAP1*,

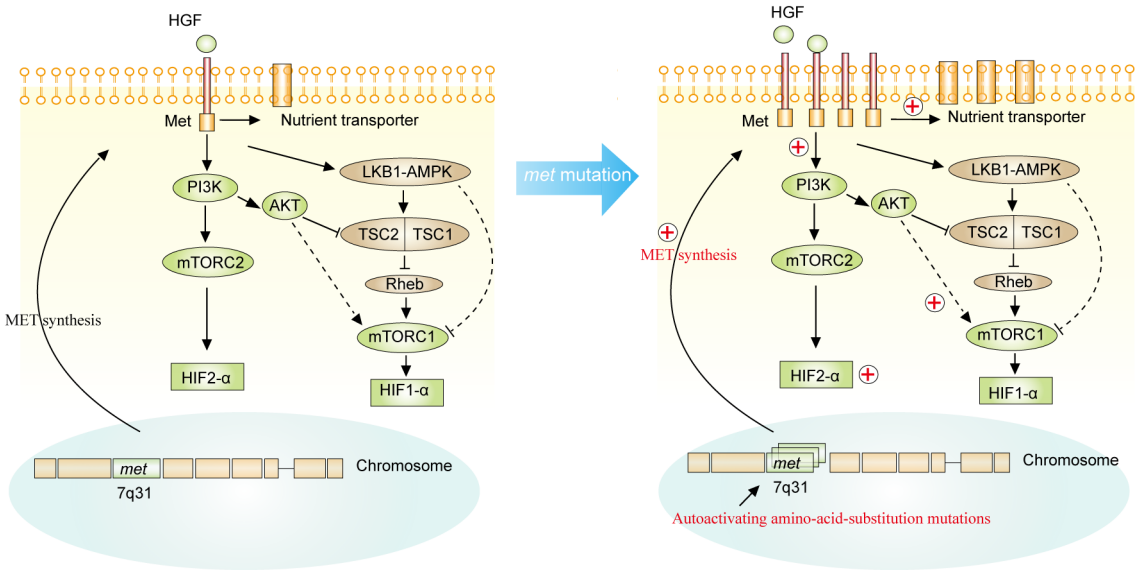

Figure 6. The genetic basis that *MET* (located on 7q31) of pRCC. *MET* mutation is duplicated, resulting in an increased dose of the gene in pRCC cases. Activation of MET will result in various changes in the signaling pathway biology. First, activation of the phosphatidylinositol 3-kinase (PI3K) signaling pathway by the activation of MET will promote cell surface expression of nutrient transporters, which increases the uptake of amino acids, glucose and other nutrients. Second, activation of MET can enable PI3K to activate mTORC2 with subsequent activation of HIF2-α. Third, activation of MET can act on mTORC1 and subsequently HIF1-α via activating AKT (activating) or the LKB1-AMPK and TSC1-TSC2 complex pathway (inhibiting). LKB1 (also referred to as STK11, serine threonine protein kinase 11) is the upstream kinase of 5' AMP-activated protein kinase (AMPK). The TSC1-TSC2 complex is a heterodimer consisting of hamartin and tuberin encoded, respectively, by TSC1 and TSC2. The complex acts as a GTPase-activating protein toward Rheb. A Ras-family GTPase can activate mTORC1, but it acts on Rheb is to inhibit mTOR activity. Akt, proto-oncogene c-Akt; AMPK, 5'-AMP-activated protein kinase; HGF, hepatocyte growth factor; HIF, hypoxia-inducible factor; LKB1, serine-threonine protein kinase 11; MET, hepatocyte growth factor receptor; mTOR, serine-threonine protein kinase mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; Rheb, GTP-binding protein Rheb; TSC, tuberous sclerosis complex; +, Positive Activation.

SETD2, and other related genes, is common in RCC, in which the mutation features of these genes can be considered as important codrivers of this disease. Nevertheless, the specific mechanism by which mutations of chromatin-modulating genes results in the pathogenesis of ccRCC is unknown. Interestingly, both *VHL* and these chromatin remodeling genes are all located on chromosome 3p, and ccRCC has been regarded as a disease of 3p loss, even if the links between *VHL* and chromatin-remodeling genes are unclear[6].

Genetic alterations in pRCC and other RCC pathological types

The *Met* gene located on chromosome 7 was identified as a characteristic genetic mutation in pRCC[3]. *Met* encodes MET, a receptor tyrosine kinase that is capable of being activated by hepatocyte growth factor (HGF)[3]. Unlike the VHL mutation in ccRCC, the *MET* mutation is a duplication, resulting in an increased dose of the gene in pRCC cases[103]. The *MET* mutation is frequent in hereditary pRCC, where the MET receptor tyrosine kinase domain is subjected to auto-activating amino-acid-substitution, resulting in duplication of the *MET* gene[104]. Activation of MET will result in various changes in the biological signaling pathway. First, activating the phosphatidylinositol 3-kinase (PI3K) signaling pathway caused by the activation of MET will promote cell surface expression of nutrient transporters, which increases the uptake of amino acids, glucose and other nutrients[105]. This change promotes cell proliferation or tumor progression. Second, activation of MET can enable PI3K to activate mTORC2 with subsequent activation of HIF2-α[106]. Third, activation of MET can act on mTORC1 and subsequently on HIF1-α via activating AKT (positively activating) or the LKB1-AMPK and TSC1-TSC2 complex pathway (negatively activating) [107]. LKB1 (also referred to as STK11, serine threonine protein kinase 11) is the upstream kinase of 5' AMP-activated protein kinase (AMPK) (Figure 6)[106].

The TSC1-TSC2 complex is a heterodimer that consists of hamartin and tuberin, respectively, encoded by *TSC1* and *TSC2*. The complex acts as a GTPase-activating protein toward Rheb. A Ras-family GTPase can activate mTORC1, but it action on Rheb is to inhibit mTOR activity[107]. Consequently, the effect of the *MET* mutation on the TSC1-TSC2 complex signaling pathway is to inhibit mTORC1 and HIF-α. Loss of *TSC1* and *TSC2* in RCC will result in inhibition of mTOR and HIF accumulation by activating mTORC1 and promoting tumor progression (**Figure 6**)[108]. Activating HIF2-α and HIF1-α have been suggested to affect angiogenesis, glycolysis and metastasis of cancer cells. Inhibitors of the PI3K, AKT and mTOR pathways presumably have anti-tumor effects[109]. In addition, various other gene mutation are involved in the occurrence and development of nonccRCC. In pRCC, in addition to the *MET* mutation, genetic mutations in *NF2*, *SLC5A3*, *PNKD* and *CPQ* have been found. *TP53*, *PTEN*, *FAAH2*, *PDHB*, *PDXDC1* and *ZNF765* gene mutations were identified in chRCC[110]. These mutant genes are more or less involved in the development and progression of the related renal cancer types.

Metabolic disease concept in renal cancer

Traditionally, cancer has been regarded as a disease of uncontrolled cell proliferation mediated by oncogenes, while the metabolic disease concept of cancer has developed gradually as research has revealed metabolic pathway alterations in cancer[111-113]. Recently, kidney cancer may be considered a metabolic disease as a result of many of metabolic alterations in cancer, including several classical metabolic pathways[112]. These featured gene

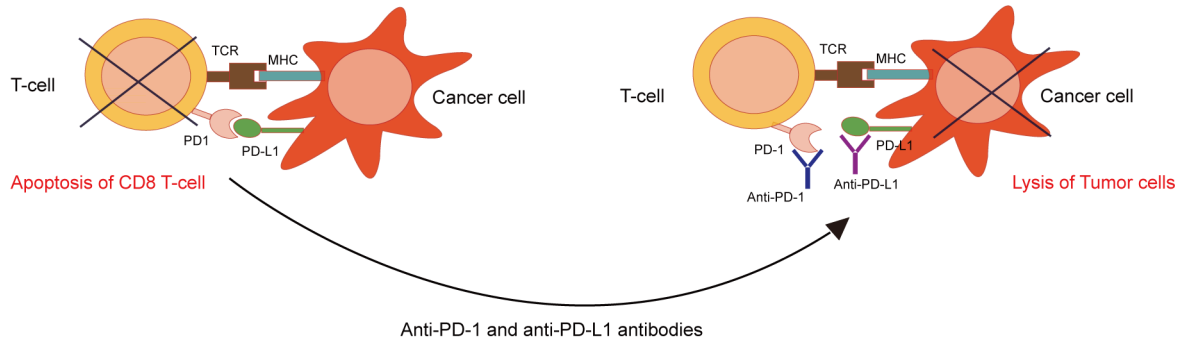

Figure 7. The programmed death-1 receptor (PD-1) pathway. PD-1 participating in T-cell binding to PD-L1 (programmed death-1 ligand) expressed on cancer cell is able to promote apoptosis of T-cells (CD8+). Anti-PD-1 and anti-PD-L1 antibodies are able to block the combination PD-1 and PD-L1 to inhibit apoptosis of T-cells (CD8+) and result in lysis of tumor cells. MHC, main histocompatibility complex; PD-1, programmed death-1 receptor; PD-L1, programmed death-1 ligand; TCR, T cell receptor.

alterations in kidney cancer are directly linked to oncogenetic mutations[113, 114]. Such as loss of *TSC1/2* leads to the Warburg effect and glutamine addiction via activating mTOR. VHL proteins can inhibit the Warburg effect via deactivation of HIF. LKB1 is associated with the upregulation of glycolysis and β-oxidation and downregulation of lipid synthesis via activation of AMPK[7]. Increasing GLUT-1 levels have been demonstrated in ccRCC samples compared with its normal control tissues, indicating that glucose uptake is increased in ccRCC[115]. Increased levels of glycolysis metabolites and enzymes such as phosphoglycerate kinase, hexokinase, pyruvate kinase 2, and LDH-A were identified in ccRCC cells and tissues in metabolomic, transcriptomic, proteomic, and transcriptomic research[116-118].

It has been suggested that the upregulation of glucose utilization for lactate fermentation is the sine qua non of the Warburg effect. Loss of *VHL* in ccRCC can increase HIF-1α, which is able to increase the expression of GLUT-1 to promote glucose uptake in cells[115]. Increased glucose can promote the TCA cycle, which is mediated by some rate-limiting enzymes including succinate dehydrogenase (SDH), fumarate hydratase (FH) and malate dehydrogenase. The TCA cycle was found to be significantly downregulated between succinate, fumarate and malate in kidney cancer compared with normal kidney tissues[116-119]. Succinate dehydrogenase (SDH) and/or fumarate hydratase (FH) deficiency can result in specific downregulation of the TCA cycle. SDH deficiency has been found to be related to familial paraganglioma and familial pheochromocytoma, and FH loss is associated with HLRCC[120, 121].

It has been reported that the PI3K-Akt-mTOR pathway is negatively regulated by PTEN and TSC1/2 and has a positive effect on mTOR, which increases the activity of anabolic pathways such as protein, lipid, and nucleotide synthesis in 28% of patients with ccRCC[94, 122]. Inactivation of the negative regulation of mTORC1, TSC1 and TSC2 results in an increased risk of ccRCC [122].

In addition, fatty acids and glutamine, arginine, and tryptophan metabolism abnormalities are associated with ccRCC. Fatty acids are elongated and desaturated by stearoyl-CoA desaturase (SCD1), which is increased in ccRCC tissues and is required for the growth and survival of ccRCC cells[123]. Studies have reported that glutamine utilization is increased in ccRCC compared with normal kidney tissues. Argininosuccinate synthase-1 (ASS1), the rate-limiting enzyme in tryptophan metabolism, is lost in tumor cells and highly expressed in normal proximal tubule cells[124]. Mutations in these key enzymes are associated with kidney cancer and thus may represent targets for therapeutic research in the clinic and lab.

Role of the immune system in RCC

The cytotoxic part of the immune system plays a vital role in the recognition and subsequent rejection of several different types of cancer. The cancer cell itself develops a system to escape the cytotoxicity of the immune system, notably the programmed death-1 (PD-1) pathway. The PD-1 pathway has been extensively valued by researchers in kidney cancer in recent years[125].

Normally, cytotoxic T lymphocytes (CD8+ T cells) recognize "foreign antigen" presented on the surface of cancer cells, which leads to the activation of cells and subsequent release of cytokines such as interferons, interleukin-2, and tumor necrosis factor. These cytokines are directly related to the death of the cancer cells. The cytokines and cytotoxic T lymphocytes can be regarded as therapeutic targets in ccRCC due to this type of cancer having features of immune T-cell infiltration. The PD-1 receptor is located in the cell membrane of CD8+ T cells, while programmed death ligand-1 (PD-L1) is presented on the surface of antigen-presenting cells and certain malignant cells, including RCC cells. The combination between the PD-1 receptor and its ligand PD-L1 has a biological effect on suppressing the cytotoxic immune system through inducing apoptosis of cytotoxic T lymphocytes. Thus, the effect of the PD-1 receptor and PD-L1 combination is anti-immune[126]. In several cancer types including ccRCC, PD-L1 is expressed on the cell surface, which can allow these cancer cells to reject the cytotoxic immune response via inducing apoptosis of cytotoxic T lymphocytes. Accordingly, some new agents, such as anti-PD-1 or anti-PD-L1 antibodies that block PD-1 and PD-

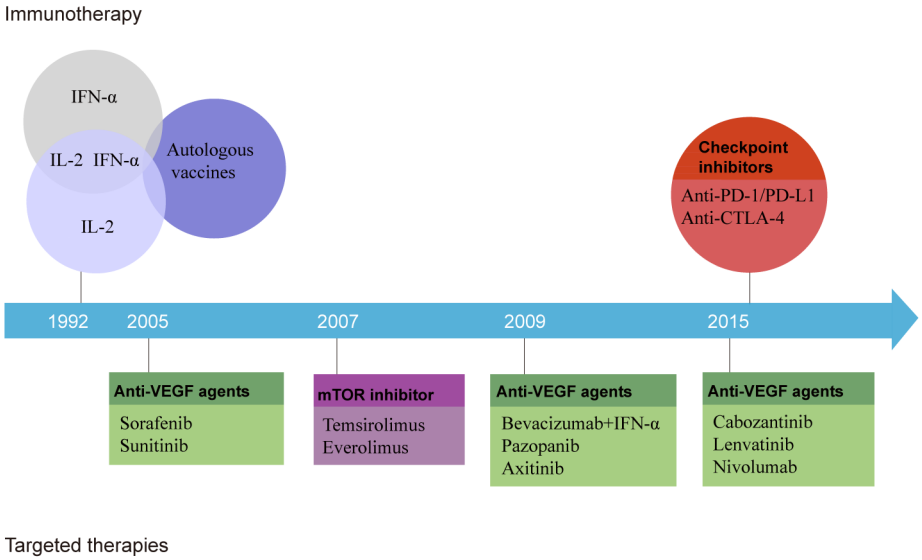

Figure 8. Therapeutic evolution of immunotherapies and targeted therapies in renal cell carcinoma.

L1, have been developed to treat cancer including ccRCC due to their effect on inhibiting the anti-immune response in cancer with PD-1/PD-L1 (**Figure 7**). PD-1 blocking antibodies include nivolumab and pembrolizumab, and PD-L1-blocking monoclonal antibodies include atezolizumab and avelumab[127]. Another protein receptor, CTLA-4, is present on the surface of cytotoxic T lymphocytes and exhibits an anti-immune function similar to the PD-1/PD-L1 pathway. The corresponding inhibitors, including ipilimumab, are under investigation with promising result for the treatment of metastatic RCC[126, 128].

Management of RCC

Surgery

Surgical treatment remains the first considerable cure for patients with surgically resectable RCC. Different surgical procedures (elective partial nephrectomy: PN, radical nephrectomy: RN, and focal therapy) are recommended to treat RCC of different clinical stages[129, 130]. PN is to remove the primary tumor while preserving those renal tissues with normal function. Traditional radical nephrectomy (RN) is to remove the tissues of these organs, including the kidney, perirenal fat tissue, adrenal gland and regional lymph nodes. Current guideline recommends PN as the standard management for clinical T1a (cT1a) renal tumors (≤4.0 cm)[131]. RN is preferred for clinical T1b (cT1b) renal tumors (>4.0 cm to <7 cm), while PN is favored over RN in the patients if technically feasible[132]. Nevertheless, RN is known to treat cT2 renal tumor, but there is evidence that some cases of T2 renal tumor may be selective for treatment with PN[133]. PN and RN mainly focus on these local renal tumors, and for metastatic RCC, cytoreductive nephrectomy with postoperative adjuvant therapy is usually applied. Small renal masses (<3 cm) can be treated with focal therapy using percutaneous, laparoscopic or open approaches. Cryoablation of the local renal mass using liquid argon or nitrogen with different freeze-thaw cycles results in the denaturation and destruction of the tumor tissue. Whole kidney removal (such as open RN) was regarded to have a better effect in terms of oncological outcome in the past, but it results in the loss of some health kidney tissue[129]. A recent Cochrane review identified that PN may be associated with a decreased time-to-death of any cause, even though it is unable to reduce surgery-related mortality, cancer-specific survival and time-to-recurrence[134]. How to select the suitable case of renal tumor remains vital for clinicians to treat renal cancer.

Minimally invasive surgical technology has developed rapidly, and there are various surgical techniques used in the clinic including open, laparoscopic and robotic PN and RN. Jame et al. compared the therapeutic effects for patients with local renal tumors undergoing three different nephrectomy surgical procedures, including open, laparoscopic and robotic PN. They found that robotic PN was more effective than laparoscopic PN as a minimally invasive approach due to its more significant centralization compared with the more uniform distribution of open PN and polarization of laparoscopic PN surgeon experience[135, 136]. The application of robotic and laparoscopic PN is able to decrease the risk of blood transfusion and length of stay compared with open PN. In addition, robotic PN can reduce the risk of inpatient complications. Nevertheless, robotic PN significantly increases hospital costs[135]. A review by Ng et al. showed that laparoscopic PN reduced renal ischemia time and exhibited other functional outcomes equivalent to open PN[137]. An updated meta-analysis has shown that robotic PN favors patients compared with laparoscopic RN in terms of perioperative outcomes of estimated blood loss (EBL), length of stay (LOS) and warm ischemia time (WIT)[138]. Considering cost and effect, laparoscopic PN seems to be more suitable to the patient's burden. Minimally invasive nephrectomy, including robotic or laparoscopic RN, has been demonstrated to be more effective to treat advanced RCC in terms of reduction of estimated blood loss (EBL), transfusion rate and length of stay than traditional open RN[139]. Commonly, PN is more technically challenging to manipulate than RN. Researchers have also compared the effects of three different operative techniques on RN: open, laparoscopic and robotic RN. While they found that robotic-assisted RN increased medical costs and did not improve patient morbidity compared with laparoscopic RN[140], they did not recommend robotic-assisted RN to perform pure RN if laparoscopic RN was manipulated by the surgeon proficiently[140].

Adjuvant therapy

Adjuvant therapy of RCC consists of immunotherapy and targeted therapy. Early immunotherapy treatment strategies indicated that cytokines, including interferon-α (INF-α) and high-dose IL-2, be applied to treat metastatic RCC as a standard of care from the 1990s when anti-VEGF agents (sunitinib) were not approved by the FDA. Nevertheless, both cytokines were limited by their availability range and substantial toxicity (especially high-dose IL-2)[141]. New immunotherapy agents for cancers continue to be developed by researchers. Active specific immunotherapy has been shown to prevent tumors in in vitro studies and small trials as early as the 1990s. A randomized study was designed to identify the effectiveness of intradermal injections of a vaccine produced from 107 autologous irradiated tumor cells subsequently admixed with Bacillus Calmette Guerin (BCG) in postnephrectomy patients. The result was disappointing due to the inferior 5-year progression free survival and overall survival rate in the vaccine group compared with the placebo group[142]. Another similar study using an autologous tumor lysate vaccine (incubated with IFN-γ and tocopherol acetate but without addition of any cytokines, bacterial, or viral adjuvants) showed an improved 5-year survival probability in the patients treated with the vaccine[143]. Due to the controversial results and complexity of vaccine manufacture, vaccine application in the treatment of RCC is challenging. A new therapeutic era for cancer management is represented by immune check point inhibitors. The most prevalent studies on immune check point inhibitors have investigated PD-1/PD-L1 and CTLA4, which have been described in the above text. The combination of PD-1 expressed in T cells and its ligand (PD-L1) expressed in cancer cells has anti-tumor immune effects. Anti-PD-1 and anti-PD-L1 antibodies can inhibit the anti-tumor immune effects of PD-1 and PD-L1 and increase the anti-tumor effect of T cells. Due to the similar anti-tumor effect of CTLA4, CTLA4 inhibitors can increase its anti-tumor function. Nivolumab and pembrolizumab are humanized anti-PD-1 monoclonal antibodies that have been newly developed in 2015 to block the combination of PD-1 and PD-L1. A randomized Phase 3 study identified that nivolumab can be the standard of care in previously treated patients with advanced RCC[144]. In addition, overall survival was longer with fewer grade 3 or 4 scores in renal cancer patients treated with nivolumab than everolimus[145]. A recent study has shown that treatment with a combination of axitinib plus pembrolizumab is tolerable, suggesting a promising anti-tumor activity in patients with advanced renal cell cancer[146]. Atezolizumab and avelumab are PD-L1 inhibitors that have studied in combination with anti-VEGF agents in a recent clinical trial and demonstrated some improvement of progression-free survival (PFS) in patients with renal carcinoma[147]. Ipilimumab is a CTLA4 inhibitor that was approved by the FDA for the treatment of melanoma in 2011[148]. A study by Motzer et al. suggested that treatment with nivolumab plus ipilimumab in patients with advanced RCC was superior to sunitinib treatment alone[149]. A recent review has shown that checkpoint inhibitors show promising results, suggesting that new immune modulatory treatments will dramatically change the current management situation for RCC[8].

From the basic biology of several main types of RCC, two types of targeted therapeutic agents have been developed for extensive use in the clinic, including anti-VEGF agents and mTOR inhibitors. Since 2015, the anti-VEGF agents that have been demonstrated to be effective and approved by the FDA are sunitinib and sorafenib[150, 151]. Sunitinib is more effective to increase PFS than IFN-α in patients with metastatic renal-cell cancer[150]. Sorafenib has demonstrated more adverse events compared with placebo, even if it is effective for improving FPS[151]. In 2007, an anti-VEGF agent, bevacizumab, plus IFN-α combination treatment as a first-line treatment was demonstrated to significantly improve PFS in metastatic RCC[152]. Recently, more anti-VEGF agents targeting downstream mediators of the HIF activation pathway have been approved by the FDA for the treatment of advanced or metastatic RCC, such as pazopanib, axitinib, cabozantinib, lenvatinib and nivolumab. Generally, a single application of sunitinib, pazopanib and the combination of INF-α and bevacizumab are recommended as first-line options; axitinib and cabozantinib are approved as second-line options[153]. These agents are almost all VEGFR tyrosine kinase inhibitors (TKIs) that can inhibit various VEGFRs and other relative growth regulatory receptors[154]. mTOR inhibitors are able to block the mTOR signal pathway involved in the regulation of cell growth, proliferation, metabolism and angiogenesis. Following the previous introduction of the genetic mechanism of RCC, the mTOR signal pathway was also shown to play a role in the development and progression of RCC. Two representative mTOR inhibitors are everolimus and tesirolimus. mTOR inhibitors were approved as second-line and first-line treatment and for metastatic RCC[155]. In a comparison of anti-VEGF agents and mTOR inhibitors, a systematic review demonstrated that sunitinib might be more effective than everolimus for nonccRCC even if the mTOR signal pathway has been identified to be featured in nonccRCC[156]. These developed targeting therapy agents like anti-VEGF agents suffer from side effects, including diarrhea, hypertension, fatigue, and nausea. Anti-mTOR inhibitors have side effects hyperglycemia, hyperlipidemia, and hypercholesterolemia. More effective targeting therapeutic agents with fewer side effects remain be exploited in the future. **Figure 8** shows the therapeutic evolution of immunotherapy and targeted therapies for RCC.

Overall, according to current guidelines for RCC, PN and RN, respectively, are recommended to treat smaller local RCC (less than 7 cm) and larger local RCC (more than 7 cm). Adjuvant therapy is applied in patients with more progressive RCC such as Stage III and Stage IV RCC. Surveillance strategies and cryoablation are applied to treat the local renal mass if a PN is difficult to perform[130]. The management options for RCC of different stages are represented in **Figure 3**.

Conclusion

The global incidence of kidney cancer is increasing rapidly and is mainly distributed in developed countries. Various factors have an effect on RCC, such as race, age, sex, smoking and obesity, hypertension and the use of antihypertensive medications, acquired renal cystic disease, diabetes and urinary tract infection, nutritional factors and diet, occupation, and genetic factors. Traditionally, *VHL* and *MET* genetic mutations have been the genetic features of ccRCC and pRCC, respectively. It was recently noted by researchers that genetic mutations occur in some chromatin-modifier genes, including polybromo 1 (*PBRM1*), SET domain containing 2 (*SETD2*), BRCA1-associated protein-1 (*BAP1*), and lysine (K)-specific demethylase 5C (*KDM5C*). The metabolic disease concept in renal cancer has been noted by the researchers worldwide. The PD-1 pathway has been valued by researchers in kidney cancer in recent years, and new agents, such as anti-PD-1 monoclonal antibodies (nivolumab and pembrolizumab) and CTLA4 inhibitors (ipilimumab) were approved to treat advanced RCC. Partial nephrectomy (PN) and radical nephrectomy (RN) remain the treatment standards for T1 and T2 stage local RCC, respectively. PN can be used for T2 stage RCC in suitable cases. Even if targeted therapy such as anti-VEGF and anti-mTOR pathway agents are recommended as first-line and second-line treatments for advanced RCC, their effectiveness and side effects remain noteworthy and necessitate further studies. For translational research of ccRCC, regulation of the mutations in chromatin-modifier genes in ccRCC, the association between these gene mutation and VHL mutations, the affected metabolic

pathways and the connections among all the genetic mutation merit investigation. In addition, the future will probably represent an era of research and application of immune check point inhibitor treatment in RCC.

Conflicts of interest

The authors declare to have no conflicts of interest.

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