Genetic architecture of renal cell carcinoma: Do we have to know?

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The kidney cancers have become more commonly detected in parallel with the widespread use of cross-sectional imaging methods. According to the data of National cancer Institute, 63,920 new cases of kidney cancer occur each year and 13,860 patients die each year from this disease. The chance for five-year survival is 91.8 % in the presence of localized disease and 12.1 % in metastatic disease [1]. Consequently, metastatic disease brings about low life expectancy in addition to increased healthcare costs associated with follow-up and treatments of the patients. The clinical and histopathological classification systems used in clinical practice are insufficient to predict which kidney cancers will progress and which possess high potential for metastasis. Genome-based and molecular analyzes used in renal cell carcinomas can be used to determine high-risk patients, establish the relationship between renal cell carcinomas with low diameter and biologically aggressive cancers, determine imaging interval for the patients on follow-up, and predict postoperative recurrence. In addition, these analyzes are considered to be of use in predicting targeted therapies in metastatic disease.

Kidney cancer is one of the most fatal cancer types among genitourinary tumors. The resistance of kidney cancer to radiotherapy and chemotherapy constitutes the most important data for researching the molecular and genetic basis of this disease [2]. Treatment options for metastatic kidney cancer have changed in the last 8–10 years. The

introduction of genome-based approaches has led to prognostic markers, indicators for treatment response, determination of individual sensitivities, and prediction of risk factors. Despite the advances in the last decade, it should be known that the two-year life expectancy is <20 % in metastatic disease regardless of the treatment administered to these patients [3].

RCC represents distinct pathological entities that are distinguishable by histological subtype: clear cell RCC (75 %), type 1 papillary RCC (5 %), type 2 papillary RCC (10 %), and chromophobe RCC and oncocytoma (10 %) [4]. However, this classification is beyond the explanation of all disease-behavior models. Depending on the histological subtypes of kidney cancer, such subtypes involve specific genetic modifications. Therefore, molecular oncologic studies have aimed to provide the correlation between the respective subtype and the disease, and targeted treatments have improved, as well. In a study by Ngo et al., clarification of molecular and genetic defects in kidney cancers has been envisaged to change the diagnosis, treatment, and follow-up of the disease by instigating the development of diagnostic, prognostic, and predictive biomarkers [5]. The study by Gowrishankar et al., on the validation of a genome-based algorithm developed for kidney cancer, demonstrated that the genome-based molecular classification, which is added to the histopathological classification of kidney tumors, may be an auxiliary test [6]. “The Cancer Genome Atlas Research Network” trial investigated more than 400 tumors, which are evaluated using various genomic platforms, and 19 important genes that are significantly mutated have been found. The study has concluded that the remodeling of cellular metabolism composed of repetitive patterns in renal cell carcinoma is associated with tumor stage and severity, and there may be new perspectives and opportunities for the treatment of the disease [7].

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Another study conducted recently has found more than 3500 oncogenic gene points in a genomic analysis obtained from 101 kidney cancers [8]. The study by Varela et al. for the genomic identification of primary kidney cancer with 227 patients has found chromatin-remodeling complex gene PBRM1 in 41 % of the cases. This gene codes the BAF180 protein, and this complex is involved in DNA repair, cell proliferation, replication, and transcription control [9]. A study of genomic analysis by Yang et al. [10] with 136 kidney cancers compared expressed genes with tumor tissue and normal tissue samples. Figure 1 shows the hierarchical clustering identified in patients with tumors by using 186 different genes. The pink color represents the tissues with kidney cancer, and the blue color represents normal tissues. Green and red colors represent suppressed and non-suppressed genes, respectively (Fig. 1).

Knowing the genetic architecture of kidney cancer allows us to clarify the underlying metabolic pathways. Based on the previous studies in the literature, kidney cancer-associated mutation causes impaired regulation of at least one metabolic pathways mediated by oxygen, iron, energy, and/or nutrient sensing [11]. The most typical genetic abnormality of clear cell carcinoma is 3p deletion

(LOH 3p), which is seen in 75.8 % of the cases. Additionally, 34–56 % of sporadic cases coincide with von Hippel-Lindau disease [12]. The common endpoint resulting from *VHL*, *FH*, and *SDH* mutations is the stabilization of HIF through inactivation of PDH, driving the transcriptional activation of genes that support tumor growth, neovascularization, invasion, and metastasis [11]. Knowing the genetic architecture has caused advances in kidney cancers, as well as in the approach related to targeted treatment in recent years. Figure 2 shows the VHL pathway and targeted treatments.

Drugs targeting the VHL pathway have been approved for treating patients with advanced kidney cancer. However, even Sunitinib used in this area has a partial response success of only 31 %. Although progress in this area is pleasing compared to interferon, most of the advanced kidney cancer patients who are treated with targeted agents eventually suffer progression. Unfortunately, a long-term complete response is achieved in very few patients [11]. Failure of the available therapeutic treatments has resulted in the need for new therapeutic approaches to this type of tumor. The discovery of STF-62247, a novel agent selectively targeting autophagy in clear cell kidney cancer that involves

Fig. 1 Suppressed and non-suppressed genes in normal and cancer tissues [10]

Fig. 2 The putative role of VHL–HIF–EPO pathway in RCC progression (Morais et al. *BMC Cancer* 2013 **13**:14. doi:10.1186/1471-2407-13-14)

a VHL gene defect, is an excellent example of an innovative approach to the treatment of kidney cancers devoid of VHL. The discovery of STF-62247 helps us present the great significance of metabolic disorders caused by genetic defects in kidney cancer [13]. Kidney cancer should be considered a metabolic disease based on a genetic defect. Targeting these metabolic disorders provides different approaches to the occurrence of this disease. Information obtained from the results of genomic- and molecular-based analyses in kidney cancer has allowed us to develop a different perspective about this cancer.

All papillary RCCs are characterized by trisomy of chromosomes 3q, 7, 8, 12, 16, 17, and 20 and loss of the Y chromosome. The most consistent genetic anomalies are present in both solitary and multifocal papillary RCC. 17q allelic imbalance is more common in type I papillary RCC, while 9p allelic imbalance is more common in type II papillary RCC [12]. The c-Met proto-oncogene mutation on chromosome 7 characterizes hereditary and a subset of sporadic papillary RCCs. These patients with hereditary leiomyomatosis and RCC have risks for leiomyomas

of the skin and uterus, and type II solitary papillary RCC. This autosomal dominant syndrome is caused by the FH (fumarate hydratase) gene, and this gene codes fumarate hydratase enzyme in the Krebs cycle [12]. The two best examples of a genetic and metabolic basis for kidney cancer are fumarate hydratase- and succinate dehydrogenase-deficient kidney cancers, which represent the “Warburg effect” in cancer. Under aerobic conditions, tumor tissues metabolize approximately tenfold more glucose to lactate in a given time than normal tissues, a phenomenon known as the Warburg effect [14].

In HLRCC, the kidney cancer cells that are devoid of FH have severely impaired oxidative phosphorylation and have been shown to be dependent on glycolysis for energy production. The impaired ultrastructure of kidney cancer cells in such condition has been demonstrated with abnormal mitochondria. Such FH-devoid tumor cells have significantly increased glucose transport and are extremely dependent on glucose for growth. There is an increased expression of GLUT1, which provides glucose transport, in the cell walls of such type of tumors [15]. Molecular

Table 1 Genetic and molecular findings of renal cell carcinoma

Tumor type	Chromosome	Gene	Protein	Syndrome
Clear cell carcinoma	3p25	<i>VHL</i>	pVHL	von Hippel-Lindau
Clear cell carcinoma	9q34 16p13	<i>TSC 1 TSC 2</i>	Hamartin, tuberin	Tuberous sclerosis
Clear cell carcinoma (multiple, bilateral)	3p13-14	?	?	Constitutional translocation chromosome 3
Papillary RCC	3q, 7, 8, 12, 16, 17, 20 and loss of the Y chromosome			
Type I papillary RCC	7p31	<i>c-MET</i>	HGF-R	
Type II papillary RCC	9p	?	?	
Type II papillary RCC	1q42	<i>FH</i>	FH	HLRCC
Papillary RCC, oncocytomas	1q21	?	?	Familial papillary thyroid carcinoma
Papillary RCC (multiple chromophobe RCC and oncocytic adenoma)	17p11	<i>BHD</i>	Folliculin	Birt-Hogg-Dube
Renal medullary carcinoma	1q32 and 3p25	<i>VHL</i>	? + pVHL	
Mucinous tubular and spindle cell renal cell carcinoma	2, 5, 7, 9, 10, 11, 12, 16, 17, 19, 20, 22, and X		?	
TFE3 t(X;1)(p11.2;q21.2) translocation	Xp11.2	<i>IGHM enhancer 3 (TFE3)</i>	?	
Tubulocystic carcinoma	7 and 17	?	?	
Thyroid-like (follicular) renal carcinoma	1, 2, 3, 5, 6, 10, 11, 16, and 17	?	?	
Clear cell papillary RCC	1, 2, 6, 10, 3, 7, 17, and Y	?	?	

? unknown

abnormality caused by this genetic defect may cause some practical approaches in patients. PET scans of the patients with such tumor demonstrate a characteristically high FDG uptake. This approach should imply improvement also in the treatment step of cancer. Therefore, targeting a vascular structure and impairing glucose transport in a glucose-dependent tumor may provide a novel approach to the treatment of these fatal malignancies [16]. The oncocytoma tumor is cytogenetically characterized by a massive loss of chromosomes 1, Y, 2, 10, 6, 21, 13, and 17 [17]. Twenty-seven percent of oncocytoma cases are associated with a loss of chromosome 17 and a mutation of p53, a tumor suppressor gene. Birt-Hogg-Dubé syndrome (BHD-S) is an autosomal dominant disease characterized by trichofolliculomas, trichodiscomas, and lung cysts. The BHD gene is localized on the short arm of chromosome 17 [11].

Scientists have been very excited in recent times by the fact that the metabolic pathways with defects cause impairment in the ultrastructure of mitochondria. When considered specific to kidney cancer, the genetic basis of sporadic chromophobe renal carcinomas and oncocytoma is not exactly clear; however, abnormal mitochondria are observed in such types of cancers, suggesting suppressed mitochondrial function. The mitochondrial defects shared by FH-deficient tumors, sporadic chromophobe renal

tumors, and renal oncocytomas may suggest a common approach to therapy for these tumor types [11]. Perhaps the future discussion of the literature should be: Is “mitochondrion repair” possible?

The most common genetic abnormality is 1q32 deletion in collecting duct carcinoma, renal medullary carcinoma (Bellini's duct carcinoma) with unknown molecular pathogenesis. The loss of 3p involving the VHL gene is common in this tumor, and it involves signalization and activations that are similar to the hypoxia pathway as in clear cell carcinoma. These pathways may play a role in the carcinogenesis of this type of cancer. There is inconsistency among the genetic studies about mucinous tubular and spindle cell renal cell carcinoma. Some authors reported losses involving chromosomes 1, 4, 6, 8, 13, 14, and 15, and gains of chromosomes 2, 5, 7, 9, 10, 11, 12, 16, 17, 19, 20, 22, and X. Others found no lack of the gains of chromosomes 7, 17, and Y [11]. Renal carcinomas are associated with Xp11.2 translocations/TFE3 gene fusions; these carcinomas are defined by several different translocations involving chromosome Xp11.2, all resulting in gene fusions involving the transcription factor binding to IGHM enhancer 3 (TFE3) gene. Tubulocystic carcinoma is also characterized by the gains of chromosomes 7 and 17. In the gene expression profile of thyroid-like (follicular) renal carcinoma, the gene

expression profiling showed widespread under expression or overexpression, particularly involving chromosomes 1, 2, 3, 5, 6, 10, 11, 16, and 17. Gains of chromosomes 1, 2, 6, 10, 3, 7, 17, and Y were found in acquired cystic disease-associated renal cell carcinoma and clear cell papillary renal cell carcinoma (RCC) cystic form. Clear cell papillary RCC did not show either 3p or trisomies of chromosomes 7 and 17. There are controversial genetic studies about leiomyomatous renal cell carcinoma. There are also cases with no 3p deletion detected, as reported in cases with loss of chromosome 3p [11]. Genetic and molecular findings of renal cell carcinoma are summarized in table (Table 1).

We have learned much from the literature of the genetic and metabolic basis for kidney cancer, which should enable us to predict the pathways likely to be involved in histologic types of kidney cancer with a lower incidence leading to the design of more effective therapies. It is also possible to make genomic- and molecular-based predictions for the atypical cancers for which the genetic basis has yet to be exactly elucidated. For instance, we do not know the genetic basis of rare kidney cancer types such as medullary renal carcinoma. However, we know that medullary renal cell carcinoma is associated with hypoxia. Medullary renal carcinoma is an aggressive form of kidney cancer and is seen almost only in sickle cell anemia. Sickle cell disease, an inherited disorder, develops hypoxic areas in renal parenchyma through microangiopathy. These areas have been shown to increase the levels of HIF. Therefore, the response to targeted anti-HIF treatments should not be a surprise in these patients.

In conclusion, identification of the genes for kidney cancer has provided the foundation for development of targeted approaches to therapy for patients with these disorders. Kidney cancer is a heterogeneous disease. A systematic approach to the dominant mutation of a single gene and genome-based variables will be the key to establish the somatic genetic architecture of kidney cancer.

Compliance with ethical standards

Conflict of interest Non-declared.

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