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Molecular Pathogenesis of Renal Cell Carcinoma: A Review

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1. Introduction

Renal cell carcinomas (RCC) represent almost 90% of all kidney cancers and in about 2% of cases there is a family history of RCC (McLaughlin et al, 1984). Despite their rare incidences, Mendelian hereditary syndromes with RCC have provided important insights into the molecular pathogenesis of this tumor. The cloning of susceptibility genes that are involved in familial predisposition has offered entry points into the signaling pathways that are deregulated in sporadic RCC. Sporadic RCC are extremely heterogeneous and are classified into many histological subtypes. The most frequent form is clear cell or conventional RCC, accounting for approximately 75% of all cases, whereas the most common non-clear cell tumor is papillary RCC (12% of cases), which is subdivided into types 1 and 2. Other subtypes include chromophobe and oncocytomas, each of them occurring in 4% of patients, collecting-duct (<1%) and rare forms or yet to be classified (< 2%). The correlation between histopathological features and genetic alterations in RCC has been introduced in 1997 with the Heidelberg classification (Kovacs et al, 1997). More recently, expression profiles through microarrays have been done for many of the kidney tumor subtypes and provide the evidence that their expression patterns reflect their histological classifications and demonstrate that various renal tumor subtypes are genetically distinct entities (Higgins et al, 2003).

Generally, there is a good correlation between the genetic causes of familial RCC and their histopathological features as exemplified by the commonest form of hereditary RCC, von Hippel-Lindau (VHL) disease, which invariably presents a clear cell type. Moreover, germline mutations in the *MET* proto-oncogene cause type 1 papillary RCC, whereas type 2 is correlated with germline mutations in the fumarate hydratase gene, which cause hereditary leiomyomatosis. Birt-Hogg-Dubè syndrome is also characterized by susceptibility to RCC but with a mixed chromophobe-oncocytoma histopathology, and is associated with germline mutations in the *BHD* tumor suppressor gene.

All the genes identified so far, which are involved in the molecular pathogenesis of hereditary and sporadic RCC comprise a diverse set of complex biochemical and cell metabolism pathways, such as iron, energy, nutrient and oxygen-sensing (Linehan et al., 2010a). A plenty of biochemical and molecular studies of the numerous signalling pathways

disrupted in RCC have already provided reasonable translational approaches and clinical applications of target therapy RCC with promising results (Iliopoulos, 2006). The histopathological and molecular features of RCC are summarized in table 1.

Tumor type	Locus	Gene	Pathway	Syndrome
Clear cell	3p25	<i>VHL</i>	VEGF	von Hippel-Lindau
	3p14 3p21 17p11	<i>FHIT</i> <i>RASSF1A</i> <i>BHD</i>	TGF- β AMPK- mTOR	Familial clear cell RCC Birt-Hogg-Dube
Papillary type 1 type 2	7q31 1q42	<i>MET</i> <i>FH</i>	MET-HGF VEGF TGF- β	Hereditary papillary RCC Hereditary leiomatosis
	7q31.1 9q34 16p13 1q25	<i>FRA7G</i> <i>TSC1</i> <i>TSC2</i> <i>HRPT2</i>	 mTOR mTOR	 Tuberous sclerosis complex Tuberous sclerosis complex Hyperparathyroidism -jaw tumor
Chromophobe	17p11	<i>BHD</i>	AMPK- mTOR	Birt-Hogg-Dube
Oncocytoma	17p11 9q34 16p13	<i>BHD</i> <i>TSC1</i> <i>TSC2</i>	AMPK- mTOR mTOR mTOR	Birt-Hogg-Dube Tuberous complex Tuberous complex
Collecting duct carcinoma	-1q32,-6p,-8p, -9p,-13q,- 19q32,-21q	unknown	unknown	none
Renal carcinoma associated with Xp11.2 translocation	1p34 1q21 17q23 17q25 3q23 Xq12	<i>PSF-TFE3</i> <i>PRCC-TFE3</i> <i>CTLC-TFE3</i> <i>ASPL-TFE3</i> ? <i>NonO-TFE3</i>	none	none
Mucinous tubular and spindle cell carcinoma	-8p,-9p,- 11q,+12q,+16 q+17,+20q	unknown	unknown	none

Table 1. Histopathological and genetic characteristics of RCC

2. The oxygen-sensing pathway: HIF-VHL interaction and clear-cell RCC pathogenesis

Hypoxia-inducible factors (HIF) are oxygen-sensitive basic helix-loop-helix transcription factors, which regulate biological processes that facilitate both oxygen delivery and cellular adaptation to oxygen deprivation. HIF is a heterodimer consisting of unstable α -subunits and stable constitutively expressed β -subunits. HIF- α , together with HIF- β bind to hypoxia-response elements in gene promoters to regulate the expression of genes that are involved in energy metabolism, angiogenesis, erythropoiesis, iron metabolism, cell proliferation, apoptosis and other biological processes. HIF1- α and HIF2- α mediate transcription of a number of downstream genes thought to be important in cancer, including transforming growth factor alpha (*TGF- α*), platelet-derived growth factor (*PDGF*), and vascular endothelial growth factor (*VEGF*) (Linehan et al., 2010a).

In clear-cell renal-cell carcinoma, HIF- α accumulates, resulting in the overexpression of proteins that are normally inducible with hypoxia, acting on neighboring vascular cells and promoting tumor angiogenesis. The augmented tumor vasculature provides additional nutrients and oxygen to promote the growth of tumor cells (Cohen & McGovern, 2005).

Germline mutations in the VHL gene are found in almost all families with VHL disease, an autosomal dominant condition characterized by a plenty of benign and malignant tumors (Figure 1). The most common cancer is clear cell RCC, which affects 25-30% of patients and is a major concern in disease morbidity and mortality (Maher et al., 1990). Remarkably, up to

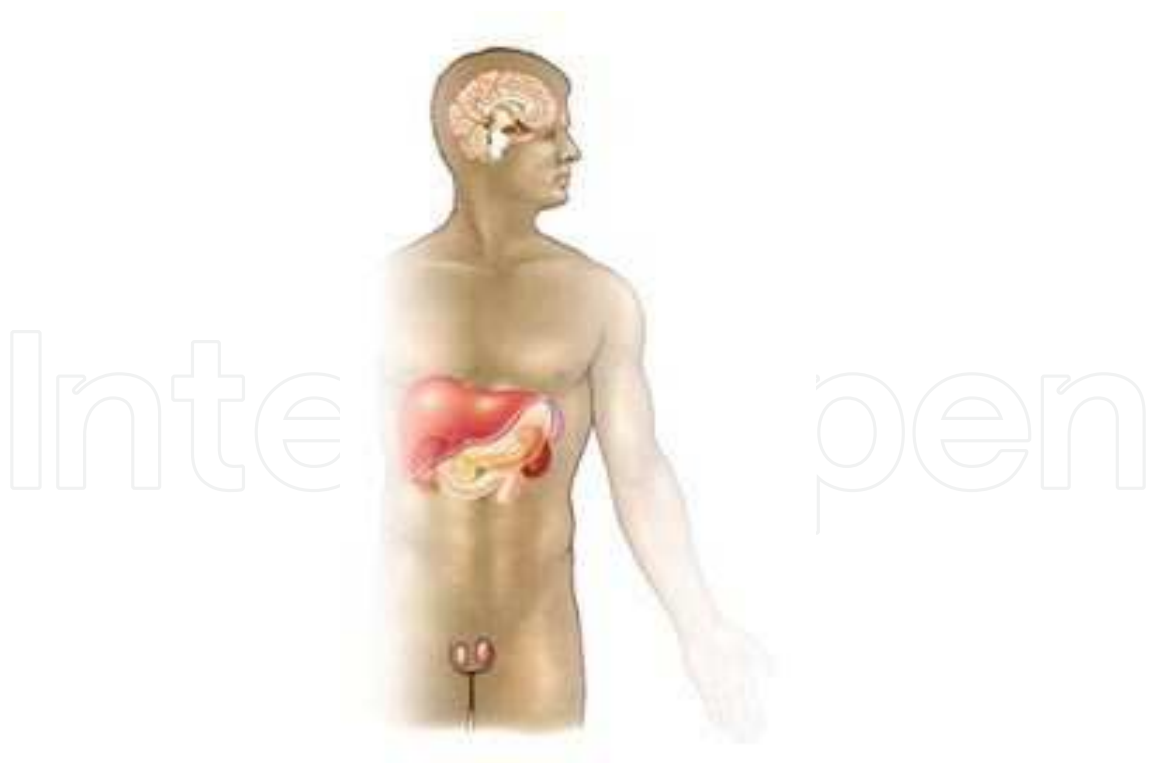


Fig. 1. von Hippel-Lindau disease predisposes to several tumors in brain, spinal cord, eyes, liver, pancreas, kidneys, testes.

91% of patients with sporadic clear cell RCC harbor biallelic VHL inactivation (Gnarra et al, 1994). Somatic mutations are found in approximately 50% of these tumors, whereas inactivation due to promoter hypermethylation has been identified in 10-20% of sporadic clear-cell RCC (Kim & Kaelin, 2004). Therefore, defects in the VHL gene are the major responsible for all cases of RCC.

The product of the VHL gene, VHL protein (pVHL), is part of an intracellular multiprotein complex that contains elongin C and B, Cul2 and Rbx1 and functions as the substrate recognition component of an E3-ubiquitin ligase. This complex selects specific substrates for ubiquitination and targets them for destruction through the proteasome, mainly HIF- α . In normoxia, the α -subunits are the target for prolyl hydroxylation that generates a binding site for pVHL. The interaction between the two proteins causes the polyubiquitynation and subsequent proteosomal degradation of HIF- α . When the cell is hypoxic or iron levels are low, the VHL complex cannot target and degrade HIF and HIF overaccumulates, driving the transcription of a number of genes important in cancer, such as *VEGF*, *PDGF*, and *GLUT1* (Figure 2a). In cells with normal VHL function, the α subunits of HIF are rapidly degraded by the proteasome, whereas in VHL-defective cells HIF- α subunits are constitutively stabilized (Maxwell et al, 1999). When the *VHL* gene is mutated, as in clear cell RCC, the complex cannot target and degrade the α subunits of HIF leading to upregulation of their targets genes (Figure 2b). Therefore, the absence of pVHL mimics hypoxia and results in a constitutive up-regulation of HIF that produces a transcriptional activation of several target genes, such as VEGF, PDGF-B, erythropoietin, TGF- α , and glucose-transporter-1 (GLUT-1).

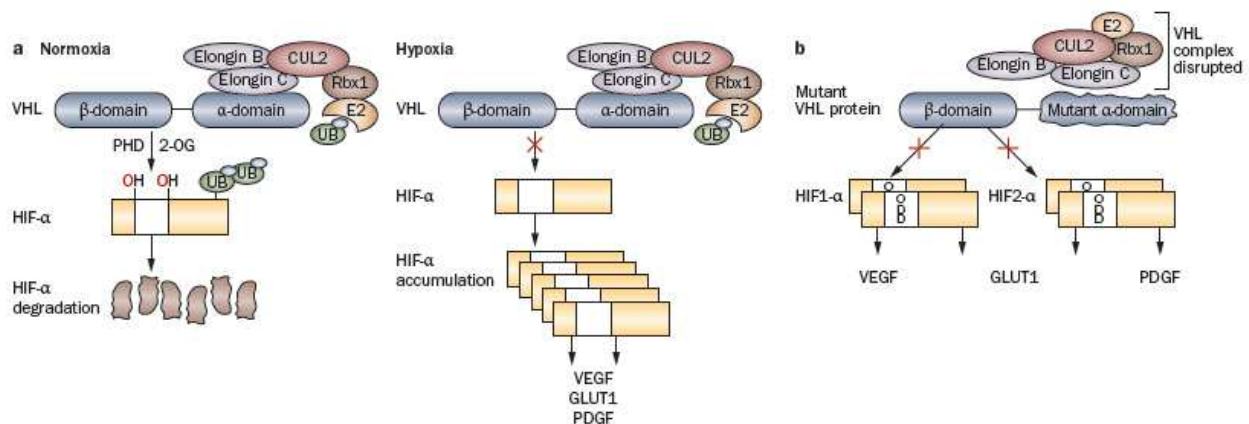


Fig. 2. The HIF-VHL-VEGF pathway. a. HIF- α degradation in normoxic cells and stabilization in hypoxic cells. b. HIF1- α and HIF2- α are not degraded and upregulate the expression of their target genes (VEGF, PDGF, GLUT1)(with permission).

It has been shown that VEGF protein expression in VHL-defective renal cancer cells is mainly induced by HIF-2 α activity. The expression of other HIF targets, such as GLUT-1, urokinase-type plasminogen activator receptor (uPAR), and plasminogen activator inhibitor-1 (PAI-1), was also regulated by HIF-2 α in these cells. Thus, HIF-2 α seems to play a critical role in tumorigenesis of clear-cell RCC mediated by loss of VHL (Kondo et al, 2002). Clear cell kidney cancers (with or without *VHL* mutation) that express both HIF1- α and HIF2- α exhibit enhanced signaling via the mitogen-activated protein kinase (MAPK) and mTOR pathways. Constitutive activation of the Raf/MEK/Erk pathway has been demonstrated in

approximately 50% of RCC samples (ref.14. EJC). Conversely, clear cell tumors that express only HIF2- α have elevated activity of the oncogene c-myc (Gordan et al, 2008).

VHL substrates other than HIF have been reported, and although their exact role in kidney carcinogenesis has not been proved to be the same as HIF's, it is possible that they may contribute directly or indirectly to VHL-deficient RCC and/or other solid tumors. VHL has been shown to interact with the RNA polymerase II subunits Rpb1, Rpb6, and Rpb7 at domains that present sequence and structural similarity to the HIF binding domain. Binding of these subunits to pVHL was shown to promote their ubiquitination and decrease transcriptional activity of Pol II (Kuznetsova et al, 2003).

Moreover, pVHL has been shown to influence the content of the extracellular matrix. Fibronectin coimmunoprecipitates with wild type but not mutant pVHL, and pVHL-deficient RCC cell lines fail to assemble extracellular fibronectin, most likely because of a defect in fibronectin maturation (Ohh et al, 1998).

Finally, it was recently shown that VHL is linked to the DNA damage response pathway. pVHL binds directly to p53, inhibits its mdm2-mediated ubiquitination, suppresses p53 nuclear export, and promotes its acetylation by p300 and overall p53 transcriptional activity. Reintroduction of pVHL in VHL-deficient RCC lines enhances p53-mediated G1 arrest and promotes their apoptotic response to genotoxic stress (Roe et al, 2006).

2.1 Therapeutic perspectives

The better understanding of VHL signaling pathway has provided the foundation for the development of therapeutic approaches that target this pathway in patients with advanced clear cell kidney cancer.

Most therapeutic agents currently approved to treat clear cell kidney cancer target either the downstream targets of HIF activity (such as the VEGF receptor) or inhibit mTORC1, which provides translational control of HIF1- α (Thomas et al., 2006). The responses to these agents observed in patients with advanced clear cell kidney cancer is proof of principle that targeting the VHL-HIF pathway can induce tumor regression in humans. However, these agents target only a small proportion of the downstream genes regulated by HIFs. An approach to target HIF transcriptional activity or translation of HIFs themselves—that is, to affect all the genes regulated by HIFs—could potentially provide more-effective therapy. Targeting the HIF2- α pathway is likely to be more successful than solely targeting the HIF1- α pathway. Efforts are currently underway to identify agents that down regulate HIF2- α -induced gene expression (Linehan et al., 2010a). Tyrosine kinase receptors trigger activation of signal transduction pathways involved in cell proliferation and survival of RCCs (Patel et al, 2006). Growth factors, such as VEGF and TGF- α , might bind to the respective tyrosine kinase receptors (EGFR and VEGFR-1) that are expressed in renal cancer cells. Thus, these receptors could potentially be targets of small molecules inhibitors. Nevertheless, many chemotherapeutic and targeted tyrosine kinase approaches are limited by their toxic effects on non-tumor cells. An alternative therapy, might be done by targeting autophagy, a central component of the cell response to nutrient and energy deprivation (Turcotte et al, 2008). By this approach, only those cells with no VHL product would be affected, whereas cells with a wild-type copy of the *VHL* gene would not. Therefore, this would provide a less-toxic and more-effective form of therapy for patients with advanced renal cancer.

3. The MET-HGF pathway and type-1 papillary renal cancer

Papillary renal-cell carcinoma occurs in several familial syndromes. Hereditary papillary renal carcinoma (HPRC) is an autosomal dominant disorder associated with multifocal papillary renal-cell carcinoma with type 1 histological features and is caused by germline activating mutations in the MET proto-oncogene (Schmidt et al, 1997) (Figure 3).

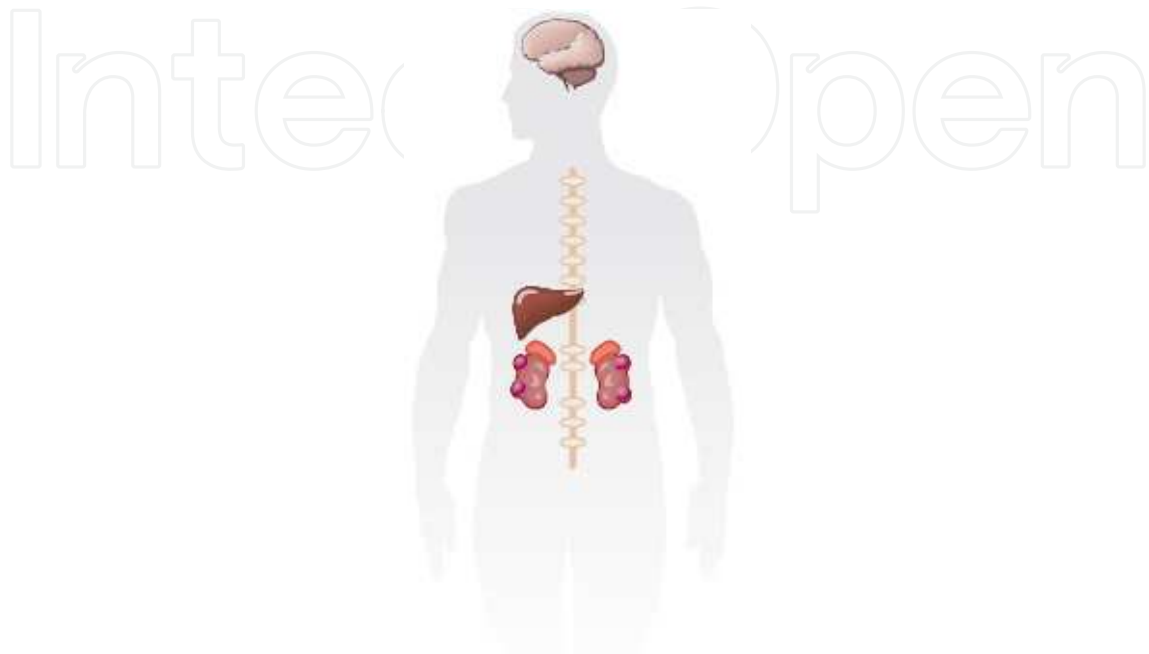


Fig. 3. Hereditary Papillary Renal Carcinoma leads to multiple (even thousands) of papillary tumors. (with permission)

The MET proto-oncogene encodes a receptor tyrosine kinase that is physiologically activated by hepatocyte growth factor (HGF). Binding of HGF to the extracellular portion of the MET receptor triggers autophosphorylation of critical tyrosines in the intracellular tyrosine kinase domain, thus activating a downstream signaling cascade. Activation of the MET/HGF signaling pathway has been shown to be involved in a number of biological activities including cell proliferation, cell motility, branching morphogenesis and epithelial-mesenchymal transition (Boccaccio & Comoglio, 2006).

Mutations of the MET proto-oncogene were detected in germline of all HPRC patients but only in a small subset of cases with sporadic type 1- papillary RCC (Schmidt et al, 1999). Thus, the pathogenesis of hereditary papillary renal carcinoma is usually different from that of sporadic papillary RCC. Tumorigenesis of most sporadic papillary RCCs are not be induced only by MET mutations, but mostly by MET and chromosome 7-related genes dosage. Since the frequency of MET mutations in sporadic papillary RCCs is low, it is possible that other genes might be involved in this form of renal cancer. In this respect, mutations of the KIT proto-oncogene have been described in 68% of papillary RCC patients (Lin et al, 2004). However, the role of KIT in the pathogenesis of this disease needs to be confirmed by functional studies. Furthermore, nutrient-stimulated HGF-MET signaling induces phosphorylation of serine-threonine protein kinase 11 (STK11 or LKB1) through the RAS-ERK pathway, implicating MET in the LKB1-AMPK-mTOR nutrient and energy sensing pathway (Figure 4).

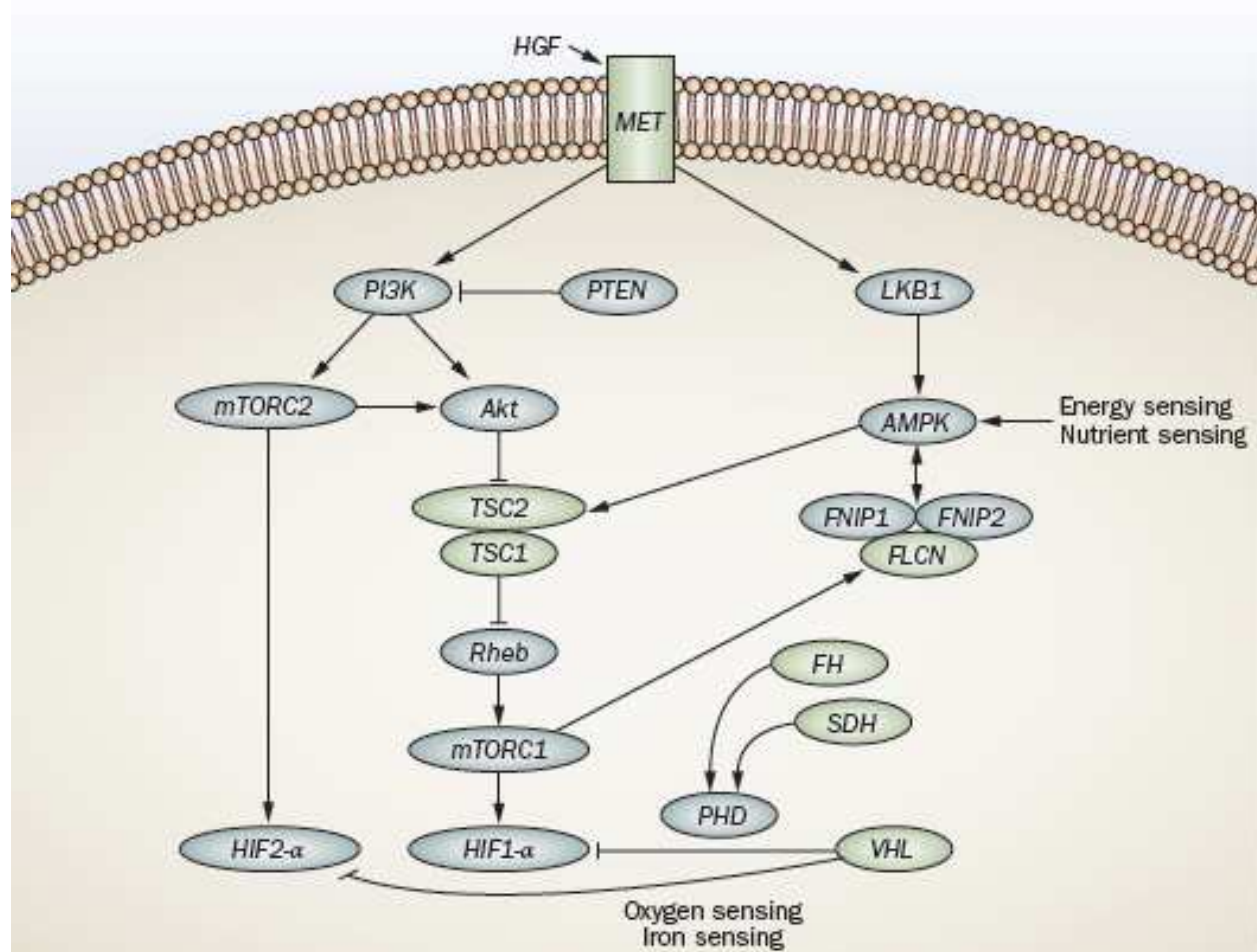


Fig. 4. HGF-MET pathway. Crosslinks between other energy, iron and oxygen-sensing pathways. (with permission)

Of particular interest for renal carcinogenesis is the observation that MET and VHL signaling pathways intersect via pVHL-mediated regulation of HIF function. HIF stabilization through hypoxia or loss of VHL function results in transcriptional upregulation, and therefore promotion of the transforming potential of the *c-MET* receptor (Pennacchietti et al, 2003). This crosstalk between VHL and *c-MET* pathways may explain why clear-cell and papillary histologies often coexist in the same tumor (Iliopoulos et al, 2006).

3.1 Therapeutic perspectives

The therapeutic implications of inhibiting *c-MET* signaling are promising, as activating mutations or copy number-overexpression of *c-MET* underlies a significant subset of type 1 papillary RCC.

A clinical trial is currently underway to determine the effect of foretinib, a kinase inhibitor of both *MET* and *VEGF* receptors, in patients with either hereditary or sporadic papillary kidney cancer. Early evidence shows the efficacy of this agent in patients with germline mutations in the tyrosine kinase domain of *MET* (Srinivasan et al, 2009). Response to such an agent with activity against *MET* might be seen in tumors that are characterized by a

mutation in the tyrosine kinase domain of *MET*; this drug might also have some activity in tumors that have *MET* amplification (Linehan et al., 2010b).

4. The mitochondrial metabolic pathway: The FH gene and type-2 papillary renal cancer and the SDH gene

Germline mutations of the *FH* gene, which encodes mitochondrial fumarate hydratase, have been detected in most individuals with hereditary leiomyomatosis renal cell carcinoma (HLRCC), who are susceptible to develop cutaneous and uterine leiomyomas, uterine leiomyosarcoma and, most often solitary and unilateral renal tumors, which may present different histological patterns, particularly type-2 papillary RCC (Tomlinson et al, 2002) (Figure 5).

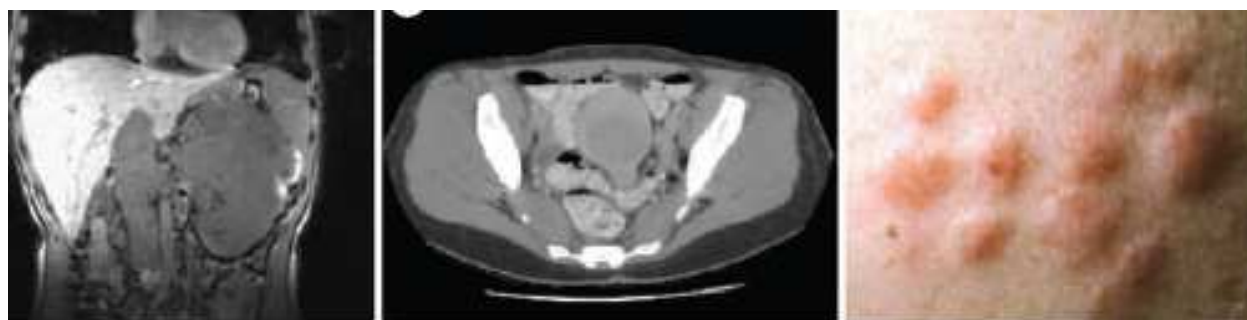


Fig. 5. Hereditary Leiomyomatosis Renal Cell Carcinoma predisposes to type-2 papillary RCC (left), uterine (middle) and cutaneous (right) leiomyomas (with permission).

FH is an enzyme component of the mitochondrial tricarboxylic acid or Krebs cycle, which has an important role in energy metabolism. In patients with *FH* deficient cells, it has been proposed that the inactivation of this enzyme might lead to a hypoxic environment that can favour renal carcinogenesis. *FH* inactivating mutations increase fumarate levels, and consequently the concentration of the fumarate precursor succinate. The high levels of succinate in the cytoplasm lead to stabilization of HIF-1 α subunits and transcriptional upregulation of hypoxia-inducible genes, such as *VEGF* and *GLUT1* (which encodes the glucose transporter type 1) (Figure 6). Thus, these factors are critically important to increase vasculature and glucose transport in RCC cells, thereby contributing to the highly aggressive nature of HLRCC-associated renal tumors (Iliopoulos et al, 2006).

The inhibition of HIF-1 α by the increased levels of fumarate provides a VHL-independent mechanism for dysregulation of HIF degradation in *FH*-deficient HLRCC-associated kidney cancers. *FH*-deficient kidney cancer cell lines are glucose-dependent and have significantly impaired oxidative phosphorylation. The glucose-mediated generation of cellular reactive oxygen species in an *FH*-deficient kidney cancer cell line results in stabilization of HIF1- α (Sudarshan et al, 2009). The impaired oxidative phosphorylation in *FH*-deficient kidney cancer results in a nearly total dependence on glycolysis for energy production.

Succinate dehydrogenase (*SDH*) is another Krebs cycle enzyme gene that has been associated with the development of familial tumors. Familial paraganglioma/pheochromocytoma kindreds have been found to have germline mutations in the mitochondrial complex II genes *SDHB*, *SDHC*, and *SDHD*. Renal carcinoma, along with

pheochromocytoma/paraganglioma, has been found to be a component of the familial pheochromocytoma/paraganglioma complex associated with germline *SDHB* mutations (Neumann et al, 2004), and a recent report described germline *SDHB* mutations in a family with renal cancer with no history of pheochromocytoma (Ricketts et al, 2008). The inactivation of SDH increases levels of succinate, which has been shown to affect HIF stability (Isaacs et al, 2005). It would be expected to severely impair oxidative phosphorylation and lead to glucose dependence of SDH-deficient kidney tumors, which are likely to be as sensitive to glucose as FH-deficient tumors (Linehan et al., 2010a) (Figure 6).

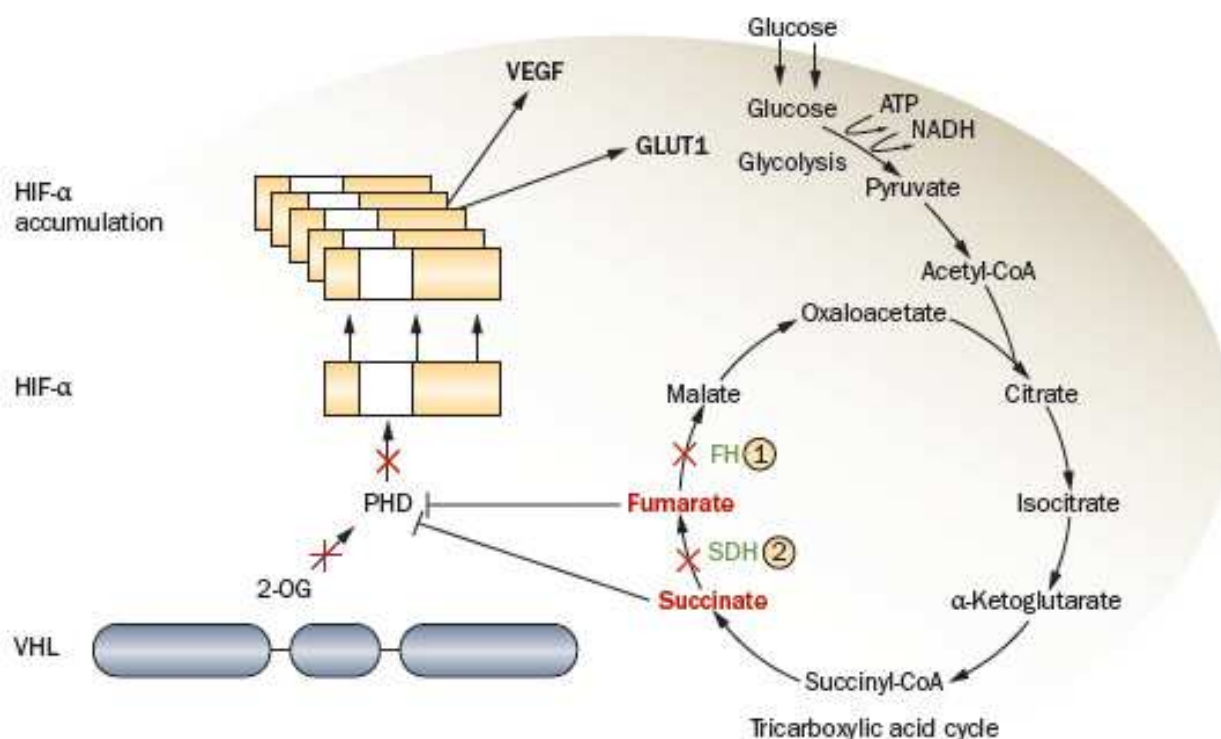


Fig. 6. FH and SDH genes and the metabolic mitochondrial pathway crosslinking with the HIF-VHL pathway (with permission).

4.1 Therapeutic perspectives

Both enhanced tumor angiogenesis and glucose transport could be the best targets for the treatment of either FH-deficient or SDH-deficient renal tumors, because they are extremely dependent on glucose transport for energy production. Whereas targeting the vasculature in patients with advanced VHL-deficient clear cell kidney cancer has only resulted in modest success, targeting the vasculature in both FH and SDH-deficient tumors could provide a powerful and effective approach to disrupt the fundamental metabolic machinery of these aggressive cancers (Linehan et al., 2010a).

5. The *FLCN* gene and chromophobe renal cell carcinomas-oncocytomas

The *FLCN* gene is impaired in Birt-Hogg-Dubè syndrome, a rare autosomal dominant disorder characterized by hair-follicle hamartomas (fibrofolliculomas) of the face and neck,

spontaneous pneumothorax, lung cysts and RCCs, particularly chromophobe RCC (33%), hybrid oncocytic renal cell carcinoma (50%), clear-cell RCC (9%) and oncocytomas (5%) (De Luca et al, 2008) (Figure 7).

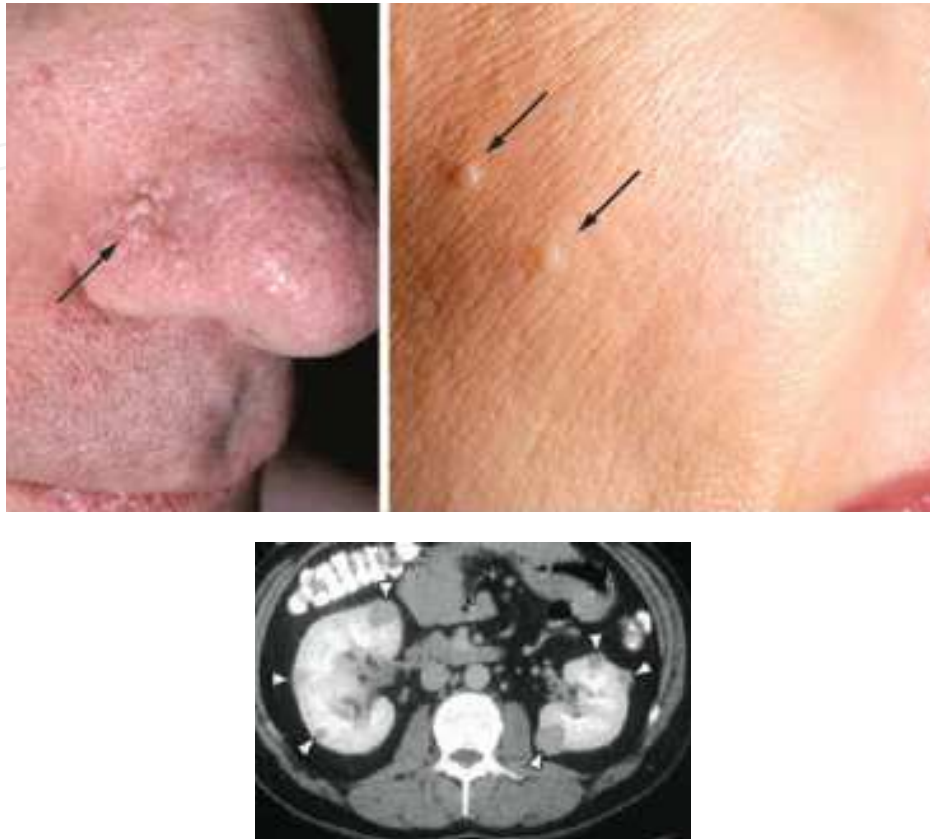


Fig. 7. Birt-Hogg-Dubè syndrome. Fibrofolliculomas on the face and bilateral RCC (with permission).

The *FLCN* gene encodes a protein called folliculin, which has no significant homology to any known human protein, although it is highly conserved across species (Nickerson et al, 2002). All described germline *FLCN* mutations are insertions, deletions, nonsense and splice-site mutations that predict truncation of the protein (Schmidt et al, 2005). In addition, somatic mutations in the second copy of BHD or loss of heterozygosity at the *FLCN* locus were observed in 70% of patients with germline mutations, thus suggesting *FLCN* to play a role as a tumor suppressor gene (Vocke et al, 2005).

In sporadic cases, somatic mutations are rare, but promoter methylation has been observed, indicating the involvement of *FLCN* in sporadic RCC tumorigenesis (Khoo et al, 2003). The function of folliculin has not been completely elucidated yet, but recent findings have showed that folliculin interacts with FNIP1, which binds to the 5' AMP-activated protein kinase (AMPK), an energy sensor that negatively regulates mammalian target of rapamycin (mTOR) (Baba et al, 2006). When folliculin functions normally, the *FLCN*-FNIP1-FNIP2 complex binds to AMPK so *FLCN* is phosphorylated by a rapamycin-sensitive kinase (mTORC1). Conversely, when folliculin is deficient, AKT, mTORC1 and mTORC2 are activated, thus stimulating tumorigenesis (Figure 8). These findings suggest a potential role of folliculin in regulating the activation of this cell survival pathway.

The research in murine models of Birt-Hogg-Dube syndrome would suggest that rapamycin analogs such as sirolimus might be potential therapeutic agents against renal tumors (Linehan et al, 2010a).

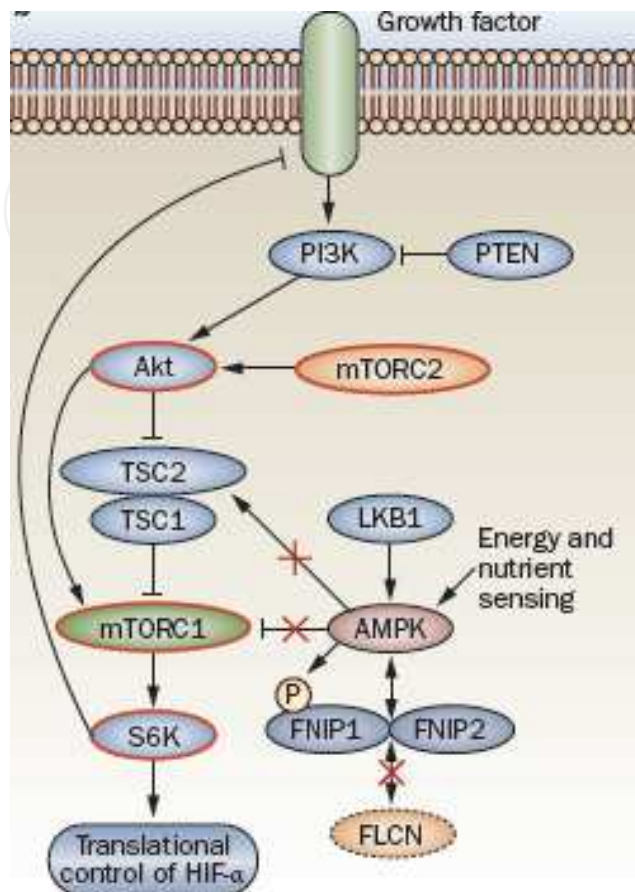


Fig. 8. FLCN interacts with AMPK-mTOR pathway. FLCN deficiency allows activation of proto-oncogenes (red circles) (with permission).

6. The AMPK-mTOR nutrient and energy sensing pathway and Tuberous Sclerosis Complex

Germline mutations in either TSC1 or TSC2 genes lead to the Tuberous Sclerosis Complex, an autosomal dominant genodermatosis characterized by multiple hamartomatous lesions that affect the skin, retina, brain, lungs and kidneys (Figure 9).

Eighty percent of children with TSC have renal lesions including benign angiomyolipomas (70%), cysts (20%), and oncocytoma (<1%) (Ewalt et al, 1998). Renal angiomyolipomas are most often multiple and bilateral, but rarely transform to a malignant tumor (<1%). The cumulative renal cancer incidence is 2.2%–4.4% (4,5) and the average age at diagnosis is 28 years, with occasional early childhood cases (Washecka et al, 1991). The renal abnormalities in TSC are unusual in patients that develop epithelial lesions, such as cysts, oncocytomas and clear cell, papillary, or chromophobe carcinomas as well as mesenchymal lesions (angiomyolipomas), suggesting that TSC genes regulate early differentiation and proliferation of renal precursor cells (Henske, 2004).

The TSC1 gene encodes hamartin and TSC2 encodes tuberin. Both proteins form a heterodimer, which interacts with many cellular pathways, including the AMPK-mTOR nutrient and energy sensing pathway. TSC1-TSC2 acts as a GTPase-activating protein toward rheb, a ras-family GTPase that activates mTORC1. GTPase activity of the TSC1-TSC2 complex on rheb results in inhibition of mTOR activity. *TSC1*-deficient and *TSC2*-deficient tumors exhibit increased phosphorylation of p70s6 kinase, s6 ribosomal protein and 4e-BP1, downstream effectors of mTORC1 activation, and readouts for initiation of mRNA translation and protein synthesis (Crino et al, 2006). Lack of TSC1-TSC2 inhibition of mTOR would presumably also result in HIF accumulation through increased *HIF* mRNA translation by activated mTORC1 (Figure 10).

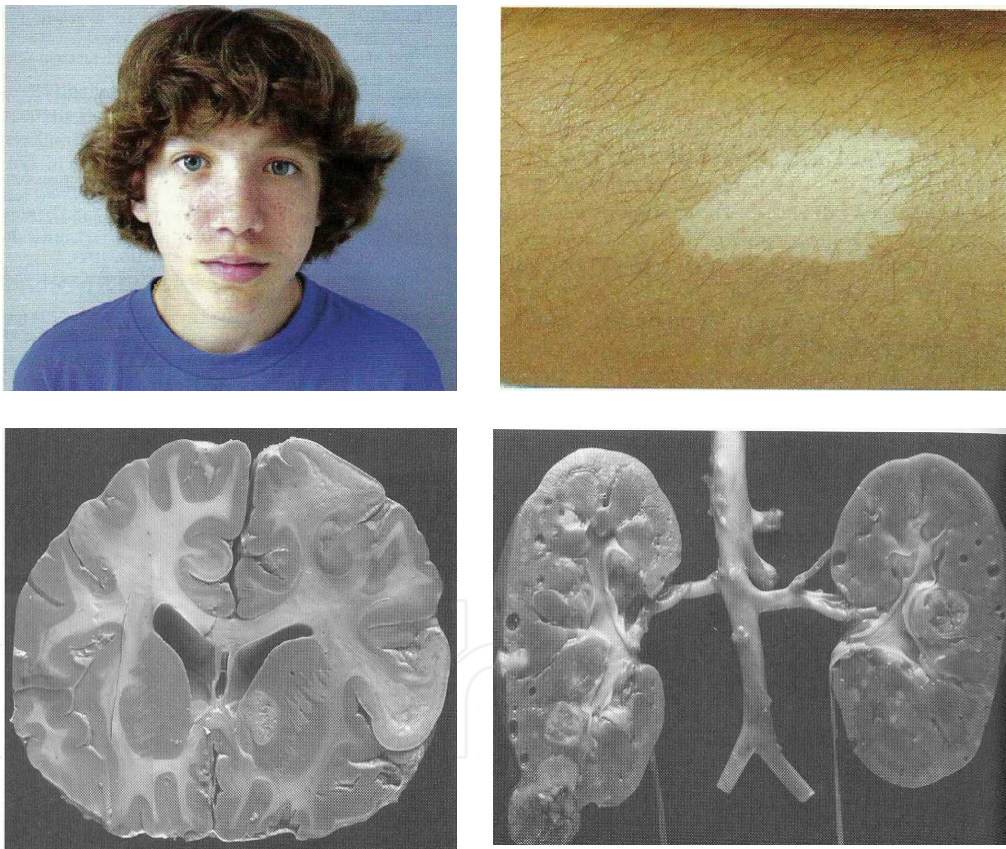


Fig. 9. Tuberous Sclerosis Complex. Hamartomatous lesions on skin (top left), hypomelanotic macules (top right), cortical tubers (bottom left) and angiomyolipomas (bottom right).

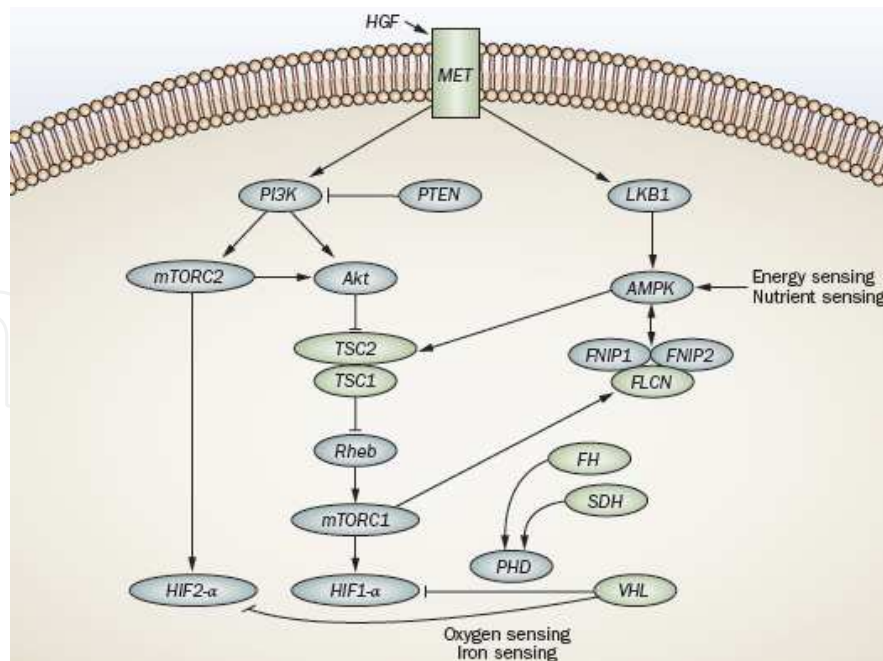


Fig. 10. TSC1-TSC2 tumor suppressor complex interacts with AMPK-mTOR nutrient and energy sensing pathway (with permission).

6.1 Therapeutic perspectives

Currently, there are a number of trials that evaluate the role of sirolimus in patients with Tuberous Sclerosis Complex. This agent has been demonstrated to cause the regression of angiomyolipomas, through the inhibition of the mTOR signaling pathway. Nevertheless, after the treatment was stopped, most renal tumors tended to growth again. In spite of that, this study provided the grounds for a molecular approach to the treatment of renal tumors associated with the *TSC1-TSC2* pathway (Linehan et al., 2010b).

7. Collecting-duct carcinomas

Collecting duct carcinomas (CDC) are uncommon and aggressive tumors thought to arise from cells of the distal nephron.

Their genetic defects have not been completely elucidated; however, they have shown cytogenetic and molecular alterations different from other renal tumors (Kennedy et al, 1990).

Nonetheless, some molecular findings suggest that these cancers are heterogeneous and can exhibit features similar to more common types of RCC as well as to urothelial carcinoma.

Genetic studies have shown monosomy of chromosomes 1, 6, 14, 15 and 22 and frequent allelic loss of 1q, 6p, 8p, 13q and 21q. Monosomy of 8p has been associated with high stage and aggressive behavior and might be responsible for the poor prognosis of CDC (Fuzesi et al, 1992). Loss of heterozygosity (LOH) of 3p is rarely detectable in these tumors, although *VHL* allelic loss has been occasionally reported. Moreover, some studies have found 9p LOH in half of CDC cases, whereas other studies have not. Mutations of the *RB* gene and LOH of 13q have also been observed in some CDC but its role in the pathogenesis of CDC needs to be clarified (Fogt et al, 1998).

8. Tubulocystic carcinomas

The molecular pathogenesis of tubulocystic carcinoma, a rare renal tumor composed of tubular and cystic structures, remains poorly understood.

The genomic defects of tubulocystic carcinoma are similar to those of papillary RCC, as it often exhibits trisomy of chromosome 17. It has been hypothesized that it may represent a lowgrade collecting duct carcinoma of the kidney despite the lack of enough cytogenetic and molecular evidence, such as trisomy of 7, monosomy of 1, 6, 14, 15, and 22, allelic loss on 1q, 6p, 8p, 13q, and 21q, which are often found in CDC (Yang et al, 2008).

9. Renal medullary carcinomas

Renal medullary carcinoma is considered as an aggressive variant of collecting duct carcinoma, a rare and rapidly growing tumor of the medulla of kidneys. This tumor is frequently seen in young male with African ancestry and carriers of sickle cell trait. In a study of nine tumors through comparative genomic hybridization (CGH), eight depicted no changes and only one presented monosomy of chromosome 22 (Swartz et al, 2002).

10. TFE translocation carcinomas family

Accordingly with the WHO classification of renal tumors (Eble et al, 2004), an entity recently defined by chromosomal translocations involving the Xp11.2 region is responsible for about one third of renal carcinomas in children and young adults. These cancers resemble clear cell RCC and seems to have a benign evolution, even with metastasis, while others may behave aggressively. They are also known as the TFE translocation carcinoma family (MTTCF) (Tomlinson et al, 1991).

All translocations result in the production of quimeric proteins containing the *TFE3* product, such as those from *PRCC*, *ASPL*, *PSF*, and *NonO* (*p54nrb*) genes. For instance, translocation of Xp to chromosome 1 forms an in-frame fusion of the *TFE3* gene on Xp11.2 to a novel gene *PRCC* on chromosome 1 (Camparo et al, 2008).

Because the normal *TFE3* protein has a DNA-binding domain, fusion proteins composed of this gene product and the ubiquitously expressed *PRCC* and *ASPL* proteins result in the overexpression of an abnormal transcription factor that causes aberrant expression of cellular genes. Another subset of renal tumors are associated with a translocation t(6;11)(p21;q12) involving the transcription factor *TFEB* (Camparo et al, 2008).

Some gene expression profiling studies indicated a distinct subgroup of tumors. For example, *TRIM 63* glutathione S-transferase A1 and alanyl aminopeptidase are the main differentially expressed genes for MTTCF (Camparo et al, 2008).

Therefore, the correct classification of these tumors may pose important prognostic and therapeutical implications. For instance, tumors with the *ASPL-TFE3* translocation particularly present at an advanced stage associated with lymph node metastases. In addition, some tumors with *PRCC-TFE3* fusion have been shown to lack a normal mitotic checkpoint control, which may turn them more sensitive to chemotherapeutic agents that target microtubules, such as vincristine and paclitaxel (Lopez-Beltran et al, 2010).

11. Mucinous tubular and spindle renal cell carcinomas

These are rare and morphologically distinctive tumors, although they share some features of type I papillary RCC.

The main molecular differences between them have been studied through CGH expression microarrays. Two studies found multiple genetic abnormalities in all cases, such as losses of chromosomes 1, 4, 6, 8, 9, 13, 14, 15, 18 and 22. The major differential diagnosis is papillary RCC with solid growth, whose gains of chromosomes 7 and 17 and losses of chromosome Y are typical, but lack in mucinous tubular and spindle RCC (Rakozy et al, 2002).

12. Renal cell carcinomas with sarcomatoid transformation

Sarcomatoid transformation has been seen in all of the common types of RCC: clear cell, papillary, chromophobe and collecting duct, but its specific molecular mechanisms remain poorly understood.

It is hypothesized that the sarcomatoid components of RCCs represent areas of dedifferentiation, and it seems that the genomic changes associated with a specific type of RCC should be conserved within the dedifferentiated sarcomatoid RCC component. In a recent study, the allelic loss profile between clear cell and sarcomatoid components of RCCs was compared and showed the same pattern of nonrandom X-chromosome inactivation in most cases. The results suggested that both clear cell and sarcomatoid components of RCCs are derived from the same progenitor cell. Some other studies suggest a link between mutation of the TP53 tumor suppressor gene and sarcomatoid morphology. Major differential diagnosis is poorly differentiated urothelial carcinoma of the renal pelvis, which presents peculiar genetic profiles, specifically, gains of chromosome 3, 7, 17 and losses of 9p21 (Lopez-Beltran et al, 2010).

13. Acquired cystic disease-associated renal tumors

Interestingly, in kidneys that have developed acquired cystic disease and, consequently, resulting in end-stage renal disease, two distinctive types of renal neoplasm have been found to occur: 'acquired cystic disease-associated RCC' and 'clear cell papillary RCC' (Cossu-Rocca et al, 2010).

Acquired cystic disease-associated RCCs are morphologically heterogeneous with abundant eosinophilic cytoplasm and variably solid, cribriform, tubulocystic with papillary architecture. Chromosomal aberrations have been found in these tumors in few studies, such as gains of chromosomes 1, 2, 6, 7, 10 and 17 (Cossu-Rocca et al, 2010).

Clear cell papillary RCC presents with papillary structures proliferating within cystic spaces, both lined by cells with clear cytoplasm. Through interphase FISH analysis, a study found all tumors to lack the gains of chromosome 7 and loss of Y, which are peculiar for papillary RCC and, in addition, there was no 3p deletion, which is typical of clear cell RCC.

The other major differential diagnoses are: tubulocystic carcinoma (trisomic for 17 but not for 7), chromophobe RCC (multiple chromosomal losses) and oncocytoma (loss of chromosome 1) (Lopez-Beltran et al, 2010).

14. Thyroid-like follicular renal cell carcinoma

Recently, there have been reports of an uncommon renal tumor, which had not been classified under a known subtype of RCC (Lopez-Beltran et al, 2010). It shows similar histology to thyroid follicular carcinoma and seems to affect more often women without previous lesions in the thyroid.

Chromosomal gains of 7q36, 8q24, 12, 16, 17p11-q11, 17q24, 19q, 20q13, 21q22.3, and Xp and losses of 1p36, 3, and 9q21-33 were identified through CGH. However, a recent report did not find any chromosomal alterations on CGH analysis. It is speculated that thyroid-like follicular RCC may represent a unique histological subtype of RCC of low malignant potential (Lopez-Beltran et al, 2010).

15. Conclusion

Currently, there is sufficient evidence that kidney cancer is essentially a disease of dysregulated cellular metabolism (Linehan et al, 2010a).

Germline mutations in each of the seven genes involved in inherited kidney cancer syndromes lead to the dysregulation of at least one metabolic pathway that is mediated by oxygen, iron, energy or nutrient sensing (Figure 11).

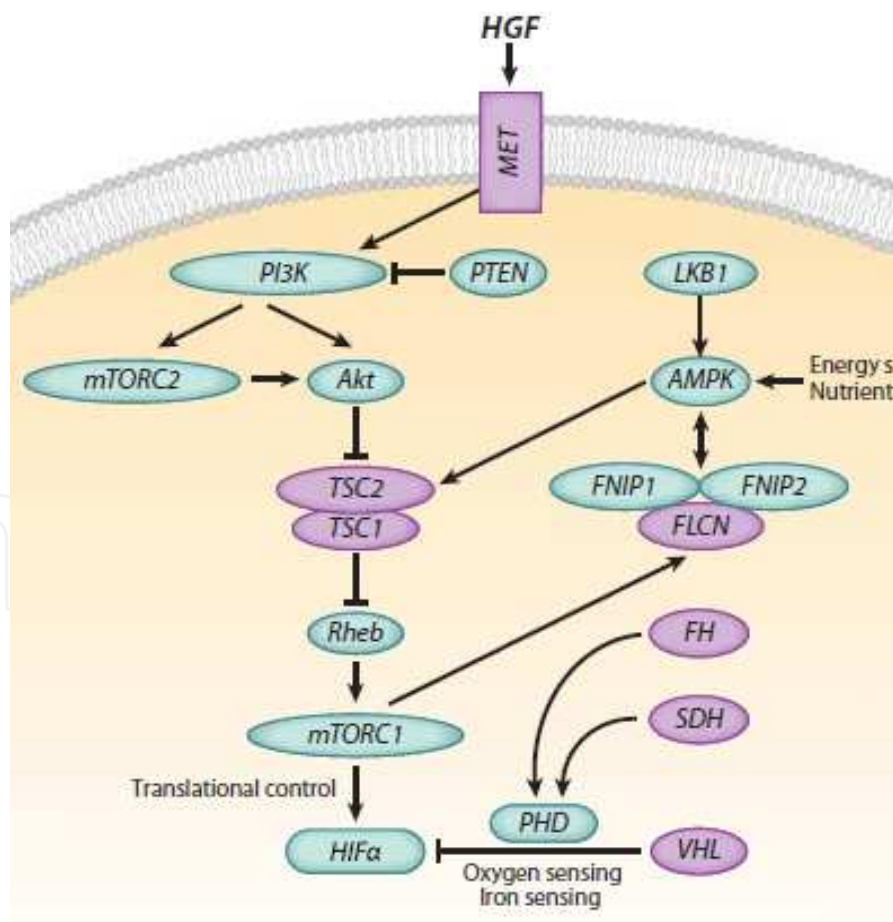


Fig. 11. The metabolic pathways mediated by the seven tumor suppressor genes mutated in hereditary cancer syndromes (with permission)

The shared consequence of *VHL*, *FH* and *SDH* mutations is the stabilization of HIFs through inactivation of the prolyl-hydroxylase domain, which leads to the transcriptional activation of genes that stimulate tumor growth, neovascularization, invasion and metastasis. HIF overexpression is also triggered by the upregulation of the mTOR pathway, either through inactivating mutations in the tumor suppressor genes *TSC1*, *TSC2* and *FLCN*, or activating oncogenic “signalling pathways”.

By targeting HIF and its downstream genes, a first-line therapeutic approach to *VHL*-deficient renal tumors may be feasible and can also be applied to *FH*-deficient and *SDH*-deficient tumors. To date, novel agents focusing on the *VHL* pathway have been approved for the treatment of patients with advanced kidney cancer (Table 2) (Linehan et al, 2010b). Unfortunately, however, most of them occasionally present progression and rarely promote long-term complete responses.

In conclusion, the pursuit of a thorough understanding of the molecular pathogenesis and the intricate metabolic pathways of advanced renal cell carcinoma may provide the foundation for the development of novel approaches that might possibly increase the response and survival rates of patients with this extremely heterogeneous disease.

Histology	Gene	Drug
Clear cell	VHL	Sunitinib, sorafenib, bevacizumab, temsirolimus, everolimus, axitinib
Type 1 papillary	MET	Foretinib
Type 2 papillary	FH	Targeting VEGF
Chromophobe Oncocytoma Hibrid oncocytic	FLCN or BHD	Rapamycin
Angiomyolipoma	TSC1, TSC2	Sirolimus

Table 2. Targeted therapies for the most common renal cell carcinomas

16. References

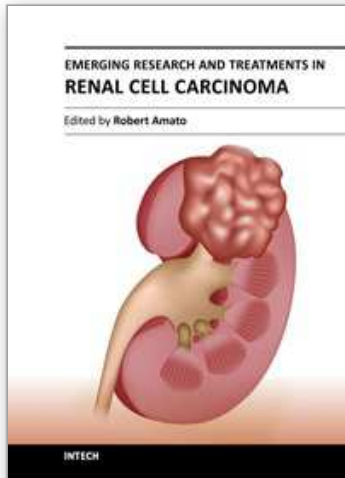
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The field of renal cell cancer has undergone a significant resurgence. This book summarizes up-to-date research and innovative ideas for the future in this rapidly changing field, which encompasses medicine, surgery, radiation oncology, basic science, pathology, radiology, and supportive care. This book is aimed at the clinician or scientist who has an interest in renal cell cancer, whether they are academic or nonacademic. The book covers tumor biology, molecular biology, surgery techniques, radiation therapy, personal testimonies, and present and future treatments of the disease that are on the horizon. The goal was to produce a textbook that would act as an authoritative source for scientists and clinicians and interpret the field for trainees in surgery, medicine, radiation oncology, and pathology.

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