Over the last two decades molecular studies of inherited tumor syndromes, which are associated with the development of kidney cancer have led to the identification of genes and biochemical pathways that play key roles in the malignant transformation of renal epithelial cells. Cancers of the kidney and renal pelvis affect about 170,000 patients per year worldwide, and result in approximately 70,000 deaths annually (data for 2008, International Agency for Research on Cancer; http://globocan.iarc.fr). For 2011 it is estimated that about 61,000 new cases will be diagnosed and approximately 13,000 patients will die from this disease in the US. Renal cell cancer (RCC) represents 2% of all cancers and about 5% of all epithelial carcinomas. The overall survival of patients with advanced disease is poor and recent progress in understanding underlying molecular mechanisms have led to the development of targeted therapies for the treatment of this disease. Morphologic criteria are used to classify renal tumors into different histological subtypes, each of which associate with certain genetic alterations that give rise to distinct molecular signatures. Clear cell RCC (ccRCC) is the most common subtype and represents about 70% of all renal tumors, 15% are chromophil RCCs, which includes papillary RCC, 5% are chromophobe RCCs and the remainder consists of collecting duct carcinomas and benign oncocytomas. ccRCC and chromophil RCCs are thought to originate from of the proximal renal tubule, whereas chromophobe and collecting duct carcinomas are derived from the distal nephron. However, recent studies of VHL-associated RCC have questioned current dogma regarding the histogenetic origin of ccRCC. Immunohistochemical studies of early ccRCC lesions suggested that von Hippel-Lindau (VHL)-associated RCCs may derive from the medullary thick ascending loop of Henle or early distal tubule. Over the last 20 years, major insights into the molecular underpinnings of renal tumorigenesis have come from the genetic analyses of families with hereditary benign and malignant renal tumors, which represent 1–4% of all cases [4]. This led to the identification of several predisposing genes, which include the VHL gene located on chromosome 3p25 (VHL disease, ccRCC), the c-MET proto-oncogene on chromosome 7q31 (type I papillary RCC), the fumarate hydratase (FH) gene located on chromosome 1q42 (Hereditary Leiomyomata and Renal Cell Carcinoma (HLRCC) syndrome, type II papillary RCC and collecting duct tumors), the Birt-Hogg-Dubé (BHD) gene folliculin (FLCN) on chromosome 17p11 (chromophobe RCC, oncocytoma), and therefore the tuberous sclerosis genes TSC1 and TSC2 on chromosome 9q34 and 16p13.3 respectively (mostly angio myolipomas, rare RCC and oncocytoma). More recently, mutations in succinate dehydrogenase genes (SDHB, SDHC and SDHD), which predispose to familial paraganglioma and pheochromocytomas, have also been detected in RCC. While mutations in most RCC-predisposing genes are rare in non-familial tumors, mutations within the VHL gene product, pVHL, are detected within the majority of sporadic ccRCCs, underscoring pVHL’s central role as a gate keeper within the regulation of renal somatic cell growth and differentiation. Major targets of pVHL are hypoxia-inducible factors (HIFs). HIFs are O2-sensitive transcription factors that mediate cellular adaptation to hypoxia, and regulate a spread of hypoxia responses, which are molecular hallmarks of RCC. These include increased angiogenic protein production, which augments O2 delivery, and metabolic reprogramming of cellular glucose and energy metabolism, which improves O2 utilization. Under normal conditions when pO2 levels are adequate, HIFs are rapidly degraded via pVHL-mediated ubiquitylation. the power to ubiquitylate HIF is lost in RCC, where HIFs are constitutively active regardless of pO2 levels (pseudo-hypoxia). This places pVHL into the middle of cellular O2-sensing, and links O2-/HIF-controlled biological processes on to renal tumorigenesis. The critical role of HIF in renal tumor formation extends beyond VHL-associated cancer, as mutations in other RCC-predisposing genes, like FH and SDH, inhibit HIF degradation and end in HIF activation. This review discusses the pVHL/HIF O2-sensing pathway within the context of renal tumorigenesis and describes recent findings that highlight HIF’s role within the reprogramming of neoplastic cell metabolism.