2. Von Hippel–Lindau syndrome: hereditary cancer arising from inherited mutations of the VHL tumor suppressor gene

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Von Hippel–Lindau syndrome (VHL) is an autosomal-dominant, multiple-tumor syndrome in which affected individuals are predisposed, over the course of their lifetime, to the formation of tumors or cysts in specific target organs such as the kidney, central nervous system (CNS), retina, adrenal gland, and pancreas. VHL is the most common syndrome of hereditary kidney cancer [1,2]. Metastatic clear cell kidney cancer and the neurologic sequelae of tumor growth in the CNS are the most common causes of morbidity and mortality of VHL patients. The VHL disease gene functions as a tumor suppressor gene (see below) [3] and places the VHL syndrome into a select group with diseases such as Li-Fraumeni syndrome, retinoblastomatosis, and familial breast–ovarian cancer, which are caused by mutations of the tumor suppressor genes p53, Rb, and BRCA1, respectively. An advance in the understanding of VHL and of sporadic clear cell kidney cancer occurred in 1993 when the gene responsible for the VHL syndrome was cloned [4].

VHL patients inherit a mutation of the VHL gene [4]. Tumors from VHL patients showed selective loss of the VHL allele inherited from the unaffected parent [5], as expected for a tumor suppressor protein (see below). Furthermore, an initial study of sporadic (i.e., nonfamilial) clear cell carcinoma identified VHL mutations in 57% of tumors, with loss of heterozygosity in 98% of those samples [6]. Further studies revealed VHL gene inactivation by hypermethylation in an additional 19% of sporadic clear cell tumors of the kidney [7]. Therefore, the VHL gene, like the Rb and p53 genes, appears to play a role in an uncommon familial cancer syndrome as well as in a common sporadic cancer. Because metastatic clear cell carcinoma of the kidney is so deadly and is currently refractory to chemotherapy and hormonal therapy [8], fresh approaches are needed. It is hoped that an understanding of the function of the VHL gene product at a molecular and cell biology level will provide new insights into the genesis and clinical behavior of clear cell kidney cancer and stimulate the rational development of effective treatments of metastatic disease.
Overview of the VHL syndrome

History

The VHL syndrome is named after Eugene von Hippel, who recognized that distinctive retinal tumors, angiomas, were hereditary [9], and Arvid Lindau, who recognized that these tumors were part of a larger ‘angiomatic lesion of the central nervous system’ [10]. Over the first several decades of this century, families were described in which affected members had not only hemangioblastomas of the retina and CNS but also cysts and tumors of visceral organs, including the kidney, adrenal gland, pancreas, and epididymis. These tumors specifically include clear cell carcinoma of the kidney, pheochromocytoma, pancreatic cystadenoma, pancreatic islet cell tumors, and epididymal cystadenomas. Melmon and Rosen coined the eponym ‘von Hippel–Lindau’ in 1964 and proposed the widely accepted criteria for diagnosis: two or more hemangioblastomas, a single hemangioblastoma associated with a characteristic visceral tumor, or a single hemangioblastoma or characteristic tumor associated with a family history of VHL [11].

The development of computed tomography (CT), ultrasound (US), and magnetic resonance imaging (MRI) in the 1970s and 1980s allowed radiographic diagnosis of silent tumors in asymptomatic individuals. These advances increased the number of identified VHL families worldwide and made detection of affected individuals within families more sensitive and reliable. During the 1970s, 1980s, and 1990s, advances in molecular biology, particularly the development of linkage analysis, made possible the identification of a location (or position) within the genome that is reliably co-inherited with specific, clinical phenotypes in autosomal-dominant diseases. The genomic position identified by linkage analysis is likely to harbor the disease gene responsible for the clinical phenotype. The disease gene can be retrieved by positional cloning. Linkage analysis requires (a) large families with many affected members and (b) sensitive and accurate means to assign clinical phenotype. These conditions for linkage analysis and positional cloning of the VHL disease gene were met only after the advent of modern imaging technology.

A hint as to the genomic location of the VHL gene first occurred in 1979 with the description of a family with hereditary clear cell cancer of the kidney [12]. Every family member who developed clear cell carcinoma had also inherited a karyotypic defect in which the short arm of chromosome 3 was disrupted by a translocation event. Subsequently, deletions of chromosome 3p were identified in sporadic clear cell carcinoma [13], further implicating the short arm of chromosome 3 as the position of a gene likely to be important for clear cell carcinoma tumorigenesis. VHL, as the most common syndrome of autosomal-dominant hereditary clear cell carcinoma, provided the best opportunity for positional cloning of a kidney cancer disease gene, and therefore research groups began studying patients from VHL families to begin the