REVIEW

Von Hippel-Lindau Disease: Current Challenges and Future Prospects

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Abstract: Understanding of molecular mechanisms of tumor growth has an increasing impact on the development of diagnostics and targeted therapy of human neoplasia. In this review, we summarize the current knowledge on molecular mechanisms and their clinical implications in von Hippel-Lindau (VHL) disease. This autosomal dominant tumor syndrome usually manifests in young adulthood and predisposes affected patients to the development of benign and malignant tumors of different organ systems mainly including the nervous system and internal organs. A consequent screening and timely preventive treatment of lesions are crucial for patients affected by VHL disease. Surgical indications and treatment have been evaluated and optimized over many years. In the last decade, pharmacological therapies have been evolving, but are largely still at an experimental stage. Effective pharmacological therapy as well as detection of biomarkers is based on the understanding of the molecular basis of disease. The molecular basis of von Hippel-Lindau disease is the loss of function of the VHL protein and subsequent accumulation of hypoxia-inducible factor with downstream effects on cellular metabolism and differentiation. Organs affected by VHL disease may develop frank tumors. More characteristically, however, they reveal multiple separate microscopic foci of neoplastic cell proliferation. The exact mechanisms of tumorigenesis in VHL disease are, however, still not entirely understood and knowledge on biomarkers and targeted therapy is scarce.

Keywords: Von Hippel-Lindau, VHL, tumor suppressor gene, neuroendocrine tumor, pancreatic tumor, pheochromocytoma, tumor formation, second hit, hemangioblastoma, renal cancer

Overview of VHL Disease

Von Hippel-Lindau (VHL) disease is an autosomal dominantly inherited tumor syndrome. The disease usually manifests in young adulthood and predisposes affected patients to the development of benign and malignant tumors of different organ systems, mainly including nervous system and internal organs. The incidence of VHL disease has been assessed as one in 36,000[1,2] and the penetrance is higher than 90%.[3]

VHL disease is named after German ophthalmologist Eugen von Hippel, who identified and described retinal hemangioblastomas,[4] and Arvid Lindau, a Swedish Pathologist, who discovered the coincidental occurrence of retinal and cerebellar hemangioblastoma with tumors and cysts in internal organs. He published the clinical spectrum of VHL disease.[5,6]

Clinically, the patients are divided into different groups: Patients with VHL type 1 predominantly without pheochromocytoma, and VHL type 2 predominantly with

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Box 1 Example of a Routine Surveillance Protocol for Von Hippel–Lindau Disease

> Annual ophthalmic examinations (direct and indirect ophthalmoscopy), beginning at age 1 to screen for retinal hemangioblastoma.
>
> Contrast-enhanced MRI brain and full spine to screen for CNS hemangioblastomas, beginning at age 12. Annual or biennial depending on manifestations
>
> MRI examinations of the abdomen every 12 months to screen for renal cell carcinoma and pancreatic tumors, beginning from the age of 12 years.
>
> Annual blood pressure monitoring and 24-h urine studies for catecholamine metabolites starting at age 4 y to screen for pheochromocytoma. Alternatively measuring plasma free metanephrines.
>
> Biennial audiogram starting at age 16 to screen for ELST

Note: Data from Maher.[204]

pheochromocytoma.[7] VHL type 2 is further subdivided into type 2A (with renal cancer) and type 2B (without renal cancer). In type 2C, affected patients develop solely pheochromocytomas.[8]

Molecular and Histomorphological Basis of VHL Disease

VHL inactivation has a variety of different effects on human tissue on molecular as well as on histomorphological levels. Since there is no animal model available to date, which has the full VHL phenotype, most knowledge is based on restricted knockout models or on observations in human tissues.

Molecular Basis of VHL Disease

Patients affected by VHL disease carry a germline mutation of the VHL tumor suppressor gene.[9] Five-hundred different pathogenic germline mutations have been identified in families with VHL disease.[10] The VHL protein (pVHL) interacts with elongins B, C and Cullin-2 to form the VBC complex, an E3 ubiquitin ligase.[11] This complex mediates ubiquitin-mediated degradation.[12–14] Biallelic inactivation of VHL is thought to be the basis of tumorigenesis in VHL disease. Reintroduction of the VHL function can reverse some effects of inactivation.[15] The consequences of VHL inactivation can be divided into HIF-dependent and HIF-independent effects ([Figure 1](#)).

HIF-Dependent Effects

HIF is a heterodimeric transcription factor consisting of an unstable α and a stable β subunit. Different HIFα genes have been identified in the human genome.[16] HIF1α and HIF2α do not appear to be fully redundant in function. Although germline knock-out of HIF1α and HIF2α results in embryonic lethality the timing and cause of death appear to differ.[17] Moreover, post-natal inactivation of HIF1α and HIF2α leads to differing phenotypes as well. The two proteins are also differentially expressed in VHL lesions, where immature cells show exclusive activation of HIF2α in contrast to frank tumors that show activation of both HIF2α and HIF1α.[18,19]

Many of the HIF-dependent proteins are involved in oxygen sensation and regulation and include genes involved in the uptake and metabolism of glucose (GLUT-1, 6-PFK, PDK), angiogenesis (VEGF, PDGF, CTGF), control of extracellular pH (CA9), mitogenesis (TGFα), and erythropoiesis (erythropoietin).[20–23] EGFR and TGFα promote cell proliferation and survival. CXCR4 and its ligand SDF1 stimulate chemotaxis and may also contribute to tumor cell invasion and metastases. MMP1 and lysyl oxidase (encoded by LOX) are implicated in ECM breakdown and tumor cell invasion/migration. Finally, dysregulation of TWIST and activation of HGFR (encoded by c-MET) are involved in epithelial-to-mesenchymal transition (EMT).

Deciphering of the molecular mechanisms of VHL functioning has had a large impact on the understanding of oxygen sensation in mammalian cells and the development of neoplasia in general.[24] The Nobel Prize in Physiology or Medicine 2019 was awarded jointly to William G. Kaelin, Peter J. Ratcliffe and Gregg L. Semenza "for their discoveries of how cells sense and adapt to oxygen availability."

HIF-Independent Effects

In addition to HIF degradation, the VHL protein is involved in HIF-independent cellular processes, which may be connected with tumorigenesis. It regulates the proper deposition of fibronectin and collagen IV within the extracellular matrix.[25] It furthermore stabilizes microtubules and maintains the primary cilium. The VHL protein also activates and stabilizes p53 and, in neuronal cells, induces apoptosis by downregulation of Jun-B.[25] Acute loss of VHL protein causes a senescent-like phenotype. It appears that it increases p400 activity, which results in inactivation (hypophosphorylation) of the retinoblastoma protein (pRb) and prevents senescence.[26] The VHL protein can also act as an adaptor to bind CK2, which inactivates the NF-kB agonist CARD9, leads to inhibition of NF-kB signaling and overall inhibits cell survival. It is furthermore needed for primary cilium function by microtubule stabilization and binding with aPKC and the polarity proteins Par3 and Par6.
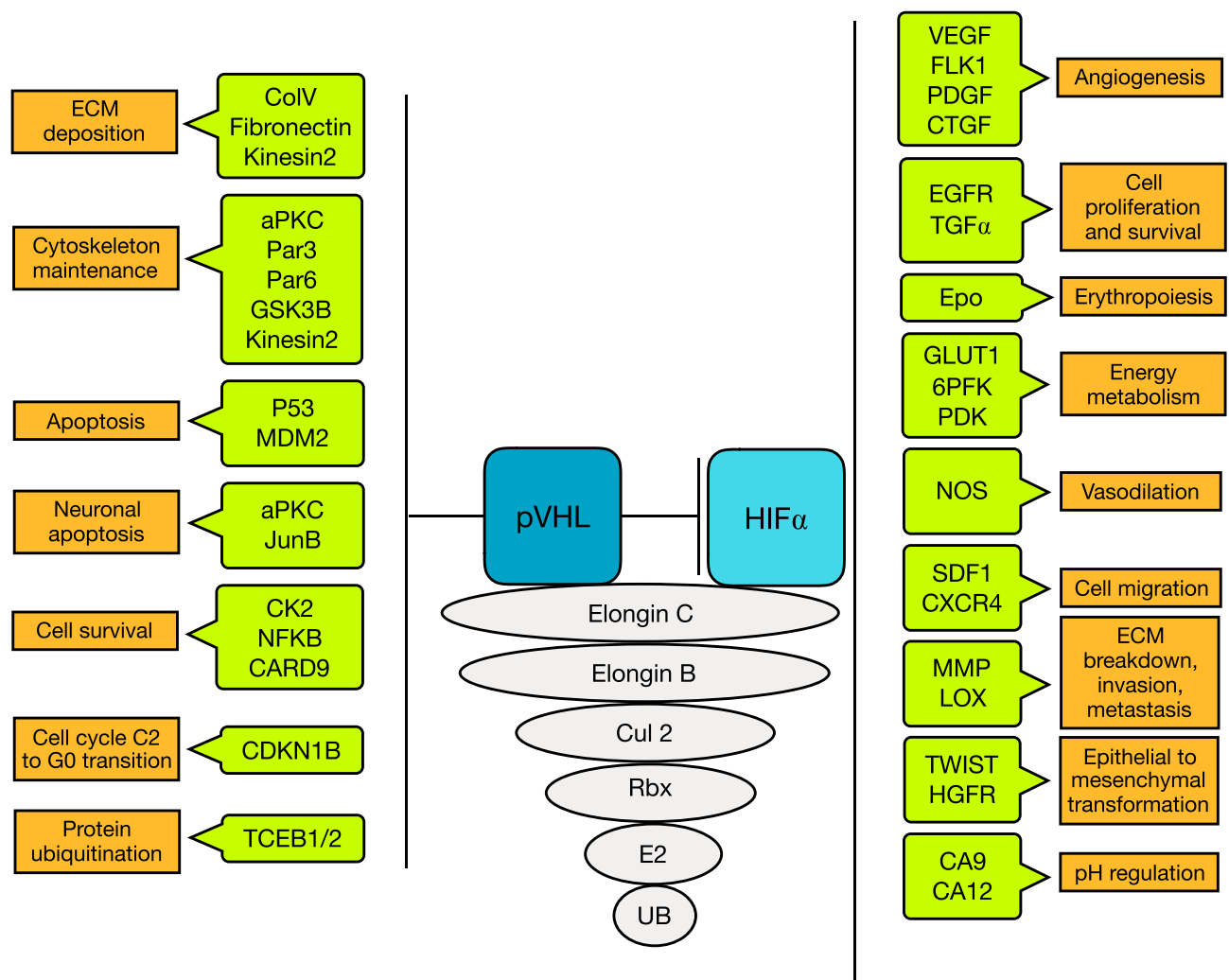
ECM deposition → ColV Fibronectin Kinesin2

Cytoskeleton maintenance → aPKC Par3 Par6 GSK3B Kinesin2

Apoptosis → P53 MDM2

Neuronal apoptosis → aPKC JunB

Cell survival → CK2 NFKB CARD9

Cell cycle C2 to G0 transition → CDKN1B

Protein ubiquitination → TCEB1/2

pVHL — HIFα

Elongin C
Elongin B
Cul 2
Rbx
E2
UB

VEGF FLK1 PDGF CTGF → Angiogenesis

EGFR TGFα → Cell proliferation and survival

Epo → Erythropoiesis

GLUT1 6PFK PDK → Energy metabolism

NOS → Vasodilation

SDF1 CXCR4 → Cell migration

MMP LOX → ECM breakdown, invasion, metastasis

TWIST HGFR → Epithelial to mesenchymal transformation

CA9 CA12 → pH regulation

Figure 1 VHL protein functions: HIF independent and HIF dependent. Abbreviations: aPKC, atypical protein kinase C; CA9/12, carbonic anhydrase 9/12; CARD9, caspase recruitment domain-containing protein 9; CDKN1B, cyclin-dependent kinase inhibitor 1B; CK2, protein kinase CK2; CoV, type V collagen; CTGF, connective tissue growth factor; Cul2, Cullin 2; CXCR4, CX chemokine receptor type 4; ECM, extracellular matrix; EGFR, epidermal growth factor; FLK1, fetal liver kinase 1; GLUT1, glucose transporter 1; GSK3B, glycogen synthase kinase 3 beta; HIF, hypoxia-inducible factor; HGFR, hepatocyte growth factor; LOX, lysol oxidase; MDM2, mouse double minute 2 homolog; MMP, matrix metalloproteinases; NFKB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOS, nitric oxide synthase; PDGF, platelet-derived growth factor; RBX1, ring box protein 1; SDF1, stromal cell-derived factor 1; TCEB1/2, transcription elongation factor B1/2; TGF, transforming growth factor; TWIST, twist related protein; VEGF, vascular endothelial growth factor; 6PFK, 6 phosphofructokinase.

The different HIF dependent and HIF-independent molecular functions imply several possible ways of how VHL related tumorigenesis may occur and which molecular targets could possibly be used for therapy. Despite the broad understanding of VHL functioning, it remains largely unclear, how a "normal" cell of a VHL patient which carries one mutated VHL allele is transformed into a tumor cell. Simple inactivation of the second VHL allele seems insufficient for tumor growth[27–29] and does also not explain the peculiar organ distribution of the disease with mainly CNS and internal organs involved. Some keys to these unsolved questions are discussed in the next section on histomorphological tumorigenesis.

Histomorphological Basis of VHL Disease

Organs affected by VHL disease may develop frank tumors. More characteristically, however, they reveal multiple separate microscopic foci of neoplastic cell proliferation. Detailed histologic studies – combined with molecular analysis – were performed on autopsy material after processing the entire anatomic structure (eg studies on entire spinal cord (Figures 2 and 3), cerebellum, epididymis (Figures 4 and 5), or vestibular aqueduct) allowing for variably precise quantitation of these neoplastic foci. Studies on both the entire VHL spinal cord and surgically resected spinal cord tumors revealed these microscopic neoplastic foci to represent early, VHL-
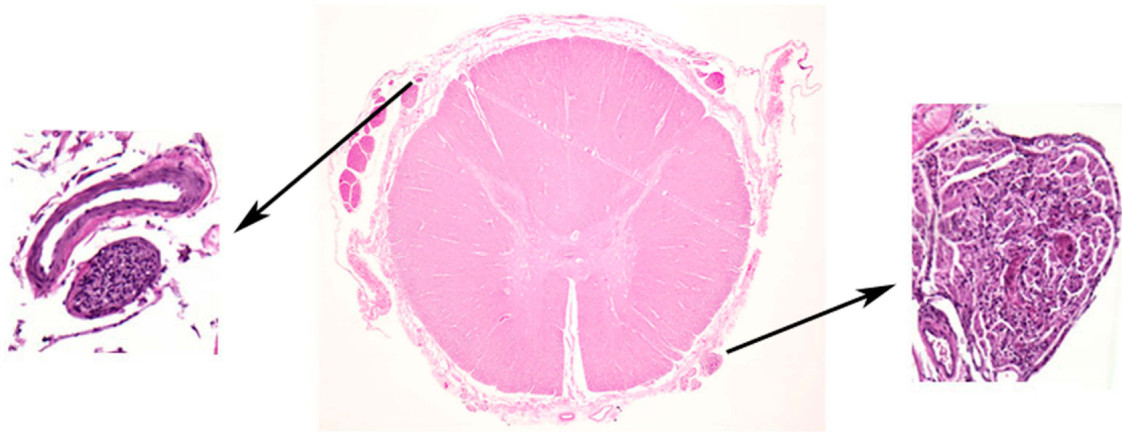
Figure 2 Early VHL pathogenesis in the nervous system: Hemangioblastoma precursors. Histologic examination of grossly normal-appearing nerve root tissue of VHL patients reveals numerous microscopic hemangioblastoma precursor structures within nerve roots. Reprinted with permission from Vortmeyer AO, Tran MG, Zeng W, et al Evolution of VHL tumourigenesis in nerve root tissue. *J Pathol.* 2006;210(3):374–382.[18]

inactivated precursor lesions. This chapter describes histologic changes occurring organs affected by VHL disease with special consideration of early tumorigenesis.

Tumors Involving CNS

Hemangioblastoma

The histology of neurosurgically resected hemangioblastomas shows a high degree of variability. Cytologically, hemangioblastomas are predominantly composed of two types of cells. The first cytologic component is characterized by conspicuous neoplastic and VHL-inactivated clear cells that are conventionally called "stromal" cells. "Stromal" cells do not exist in normal nervous system tissue, and their origin has been
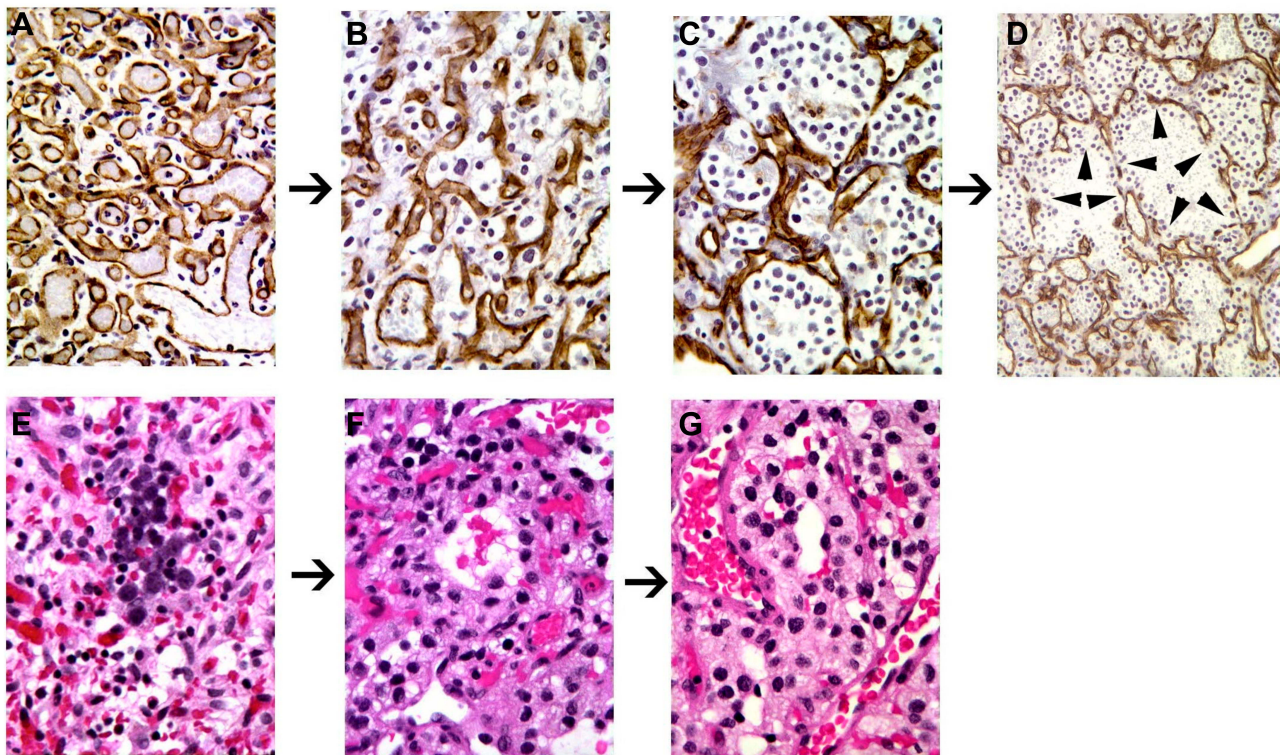

Figure 3 Hemangioblastoma progression. Proposed structural progression of hemangioblastoma from mesenchymal (**A**) to epitheloid (**B** and **C**) and vasculogenetic architecture/extramedullary erythropoiesis (**D**–**G**); (**A**–**D**), immunohistochemical stain for CD31; (**E**–**G**), (**H** and **E**) stain. Immunohistochemistry for CD31 was performed to better differentiate reactive vascular cells (positively staining cells) from neoplastic cells (negatively staining cells). (**H** and **E**) stain was performed to demonstrate erythropoiesis within epitheloid and vasculogenetic structures. Reprinted from *Exp Mol Pathol*, 96(2), Glasker S, Smith J, Raffeld M, Li J, Oldfield EH, Vortmeyer AO, VHL-deficient vasculogenesis in hemangioblastoma 162-167, Copyright (2014), with permission from Elsevier.[205]
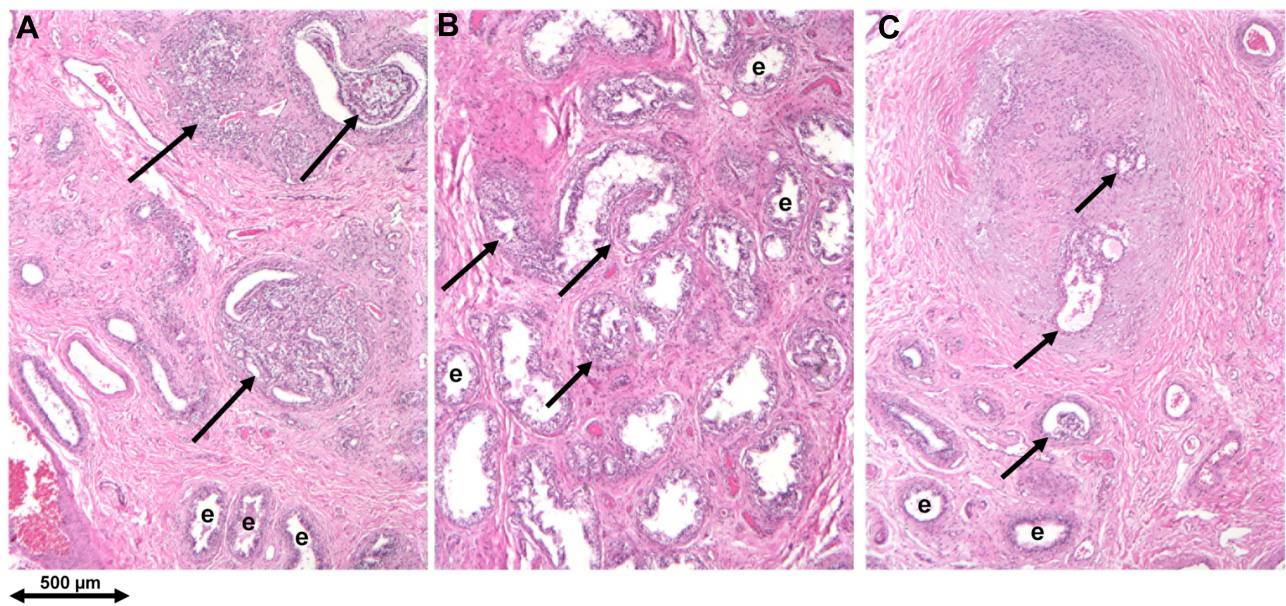
Figure 4 Early VHL pathogenesis in the epididymis: cystadenoma precursors. (**A–C**) Multifocality of cystadenoma precursor structures: "Tumor-free" VHL epididymis contains multifocal microscopic precursors in the efferent ductule compartment of the caput (marked by arrows); e= normal efferent ductules. Republished with permission of John Wiley & Sons-Books, from Epididymal cystadenomas and epithelial tumorlets: Effects of VHL deficiency on human epididymis, Glasker S, Tran MG, Shively SB, et al. *J Pathol*. 210(1):32–41. permission conveyed through Copyright Clearance Center, Inc. Copyright © 2006 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.[48]

controversial. While "stromal" cells are lipid- and glycogen-rich cells with abundant clear or bubbly cytoplasm in larger tumors, they are smaller and less conspicuous in small tumors or precursor structures. The other cytologic component of hemangioblastomas is represented by abundant blood vessels. The blood vessels do not show VHL inactivation[30,31] and therefore represent reactive angiogenesis. Intense reactive angiogenesis is a characteristic feature of hemangioblastoma

and explained by the expression of HIF, VEGF and other angiogenic factors in stromal cells.[32,33]

Hemangioblastomas show not only cytological but also marked architectural variation. Tumor cells may be scattered within a matrix of abundant capillaries, referred to as "reticular"[34] or "mesenchymal"[35] architecture. Tumors may also reveal epitheloid tumor cell clustering, referred to as "cellular"[34] or "epitheloid"[35] architecture. A transition from

Figure 5 Papillary cystadenoma of the epididymis. (**A**), Gross examination of VHL epididymis shows enlargement of the caput epididymis (white arrows). (**B**), Cystadenomas reveal papillary (pap), tubular (tu) and cystic (cy) architecture. (**C**), Immunohistochemical staining with anti-CD31 reveals extensive vascularization of the tumor stroma. Numerous reactive vascular cells are in direct contact with overlying neoplastic epithelial cells. Republished with permission of John Wiley & Sons-Books, from Epididymal cystadenomas and epithelial tumorlets: Effects of VHL deficiency on human epididymis, Glasker S, Tran MG, Shively SB, et al *J Pathol*. 210(1):32–41. permission conveyed through Copyright Clearance Center, Inc. Copyright © 2006 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.[48]

mesenchymal to epitheloid architecture occurs gradually with tumor growth. Hemangioblastomas smaller than 8 mm³ in size show exclusively mesenchymal architecture, while epitheloid features may be developed in tumors larger than 6 mm³; epitheloid features have been consistently observed in tumors larger than 737 mm³.[3,35] A markedly elevated Ki67 proliferation index in epitheloid areas suggests that epitheloid features are associated with accelerated tumor growth.[35]

Biologically, the profound cytologic and architectural transformation from mesenchymal to epitheloid tumor closely resembles stages of embryonic hemangioblastic transformation.[36] The capacity of "stromal" cells to differentiate into red blood cells has been subsequently demonstrated[37,38] and a shared protein expression profile with hemangioblast precursor cells has been identified.[28] Therefore, multiple lines of evidence have confirmed the "stromal" cells to represent hemangioblastic precursor cells.

The histologic evolution of hemangioblastomas is not completely understood. The earliest stages of VHL tumorigenesis are represented by microscopic foci, undetectable radiologically or by the naked eye. Because of their minute size, these foci can only be detected by detailed histological analysis of normal-appearing tissues of VHL patients. Moreover, to obtain information on the number and distribution of microscopic lesions, tissue blocks need to be step-sectioned at 50-micron intervals. Such studies have been performed on tissues of VHL patients that had been obtained at autopsy. Analysis of a series of cases revealed that precursor lesions of spinal cord hemangioblastomas were exclusively located in nerve root tissue, dorsal roots being far more frequently involved than anterior roots. Tumors preferentially developed from dorsal root precursors in close proximity to the spinal cord.[29,39] In general, precursor structures are detected in far greater abundance than frank tumors;[29,39] therefore, precursor structures have extremely low proliferative potential, and only a small subset of precursor structures will develop into tumors. In the cerebellum, precursors originate in the molecular layer.[19] Numerically, precursor structures are far more frequent in dorsal root tissue compared to cerebellar tissue. It, therefore, appears that precursors in the cerebellum have a higher probability to develop into clinically relevant tumor than nerve root precursors.[19]

Histologically, precursor CNS lesions reveal a sharply demarcated zone containing abundant capillaries and scattered small VHL-deficient cells;[29] by immunohistochemistry, VHL-deficient cells have revealed HIF2 activation.[39]

Significant changes occur during the progression of a precursor structure to tumor.[39] Cytologically, the VHL-deficient cells markedly increase in size and develop abundant clear, vacuolated or eosinophilic cytoplasm. While in the earliest stages of tumorigenesis VHL-deficient tumor cells show – similar to the VHL-deficient cells in the precursor lesions – a diffuse distribution pattern ("mesenchymal architecture"), further tumor growth consistently reveals tumor cells to form small clusters ("epitheloid architecture") in parts of the tumor.[35]

The retina develops from extensions of the neural tube, providing justification to include retinal hemangioblastomas among the craniospinal hemangioblastomas. Furthermore, histologic features of small and larger retinal tumors are identical to those of nerve root and cerebellar hemangioblastomas. Analogous to CNS tumors, retinal hemangioblastomas are composed of VHL-inactivated tumor cells with intense reactive vascularization[40,41] and unrelated to capillary hemangiomas occurring elsewhere in the body.

Endolymphatic Sac Tumors

Endolymphatic sac tumors were originally described by Heffner as adenocarcinomas of probable endolymphatic sac origin.[42] Endolymphatic sac tumors in VHL disease are extensively vascularized tumors forming prominent papillary structures, the papillae being lined by a single row of cuboidal epithelial cells. Cysts lined by single rows of cuboidal cells are frequently present, and epitheloid clear cell proliferation is occasionally detected.[27] Tumors larger than 10 mm in size usually present with bony erosion, while the exact border between endolymphatic duct and sac is not clearly defined, it is of clinical relevance that tumors appear to originate most frequently from intraosseous portions of endolymphatic sac/duct epithelium.[27]

Studies on clinically uninvolved endolymphatic sac and duct of VHL patients showed evidence for VHL-inactivated cells lining cysts or papillary projections; in analogy to studies in other tissues these microscopically small cystic or papillary structures may represent early stages of endolymphatic sac tumors.[27]

Visceral Tumors
Renal Cell Carcinoma

The diseased VHL kidney is characterized by renal cysts and clear cell carcinoma. These pathologic changes show wide differences in growth.[43] Histologically, solid tumors and cysts are composed of clear cells and associated with intense vascularization.[44] There is a histopathologic

continuum ranging from benign cysts and atypical cysts to carcinoma.[44] Numerically, by far the most pathogenic events in the kidney are represented by microscopic cystic and solid neoplasms.[45] VHL gene function is inactivated in the smallest foci of microscopic neoplasia.[46,47] All clear cell tumors in the kidney are designated renal cell carcinoma, although they need to reach at least 3 cm size to acquire the capacity to metastasize. Histologically, larger renal clear cell tumors may develop frankly malignant features including tumor necrosis and cytologic anaplasia with mitotic activity.

Epididymis Cystadenoma

Epididymal cystadenomas are component tumors of VHL disease composed of cuboidal epithelial cells, with papillary, tubular and cystic architecture, and prominent angiogenicity. Numerous tumor precursor elements were detected by a thorough analysis of nontumorous epididymides obtained at autopsy (Figure 4). Topographically, precursor structures were confined to the efferent ductules of the caput epididymis. Precursor structures were characterized by the formation of epithelial cysts and prominent epithelial proliferation into the lumina of cysts and efferent ductules.[48] A 3dimensional reconstruction of intraductular papillary neoplastic growth revealed the complex intermingling of pre-existent anatomic structure and slow neoplastic growth creating a hamartomatous appearance.[49] Since epididymal cystadenomas are rare neoplasms, the occurrence of bilateral tumors is highly associated with VHL disease.[50]

Papillary Cystadenoma of the Broad Ligament

Papillary cystadenoma of the broad ligament occurs less frequently than epididymal cystadenoma. Morphological and immunohistochemical features strongly overlap. Morphologic and genetic studies have established this tumor as a VHL component tumor, and it is considered as female counterpart tumor of epididymal cystadenoma.[51]

Pancreatic Microcystic Adenoma

Microcystic adenomas of the pancreas (serous cystadenomas) are tumors composed of small cysts lined by flattened or cuboidal glycogen-rich cells.[52] After the initial demonstration of VHL gene deletion and mutation in microcystic adenomas,[53] a more detailed analysis of the VHL pancreas revealed the presence of numerous small microcystic adenomas as well as VHL gene-inactivated pancreatic cysts; most cysts were of microscopic size

suggesting a continuum of development from the pancreatic cyst(s) to microcystic adenoma.[54]

Pancreatic Neuroendocrine Tumor

Pancreatic neuroendocrine tumors were established as VHL component tumors in 1998.[55] Compared to sporadic neuroendocrine tumors, VHL-associated neuroendocrine tumors more frequently exhibit clear cell morphology which may be challenging to differentiate from metastatic renal cell carcinoma or pancreatic microcystic adenoma which may occur in the same pancreas.[55]

Adrenal Pheochromocytoma and Extra-Adrenal Paraganglioma

Pheochromocytomas and paragangliomas are associated with multiple hereditary disorders. The histologic features are distinguished from other VHL disease-associated clear cell neoplasms by more variable, frequently polyhedral cytology, basophilic and finely granulated cytoplasm and cytoplasmic bodies in both familial and nonfamilial cases.[56] In contrast, analysis of VHL disease-associated pheochromocytomas revealed tumor cells with clear or amphophilic, inclusion-free cytoplasm that were more intensely intermixed with vascular cells.[57]

In conclusion, the characterization of precursor structures has provided more precise insight on the anatomic and cytologic origin of neoplastic processes associated with VHL disease. In all anatomic structures investigated so far, precursor structures were far more numerous than frank tumors. Therefore, VHL inactivation ("second hit") is necessary, but insufficient for the development of a frank tumor. In the future, comparative molecular analysis of frank tumor and precursor structures may be helpful to identify a "third hit" promoting tumorigenesis from precursor material.

VHL Disease Manifestations and Treatment

Patients affected by VHL disease develop specific types of heavily vascularized tumors in a highly selective subset of organs. Multiple and bilateral tumors occur frequently. Affected organs and lesions include retinal hemangioblastomas, cerebellar, brainstem and spinal cord hemangioblastomas, endolymphatic sac tumors, renal cell carcinomas, pheochromocytomas, pancreatic cysts, microcystic serous adenomas, neuroendocrine tumors, as well as epididymal cystadenomas.[58–61]

Retinal Hemangioblastomas

Retinal hemangioblastomas are benign tumors that frequently occur in multiplicity and bilaterally in VHL patients. Expression of high levels of VEGF in these tumors causes hypervascularization, vascular leakage and eventually retinal detachment.

Annual screening by fundoscopy and if necessary fluorescence angiography is recommended for VHL patients starting at 1 year of age. Early treatment of asymptomatic lesions is recommended. Laser coagulation or cryotherapy can control the majority of peripheral retinal hemangioblastomas.[62,63] Larger tumors can be treated by vitrectomy.[64] Optic disc hemangioblastomas should be monitored without treatment. With regular screening and early treatment of detected lesions, visual prognosis for VHL patients is in general good: In one major study approximately 8% of the eyes of VHL patients had poor visual acuity of 20/200 or worse with approx. 8% of these eyes requiring enucleation.[65]

Pharmacological treatments are in experimental stages and are discussed in the section on targeted therapies.

Craniospinal Hemangioblastomas

Hemangioblastomas are benign slow-growing highly vascularized tumors. They are frequently the first manifestation of VHL disease. These patients frequently develop multiple hemangioblastomas.[66] The hemangioblastoma tumor burden in VHL disease is associated with germline deletions and male sex.[67] Depending on their size and location hemangioblastomas cause different neurologic symptoms.[66,67] It is usually an associated pseudocyst or syrinx and not the tumor itself which causes the symptoms.[68] The syrinx is caused by vascular leakage and is frequently larger than the tumor itself.[66] Polyglobulia occurs in 10% of patients[69] and may cause thrombosis. Removal of the largest hemangioblastoma usually resolves polyglobulia.[69]

Treatment is primarily surgical and is recommended for all symptomatic tumors and for all tumors causing CSF obstruction.[66,70,71] If surgery is not possible, radiation therapy may be an alternative, however, its effectiveness remains controversial.[72–74] Pharmacotherapy of CNS hemangioblastoma is at an experimental stage and is discussed in the section on targeted therapy.

Endolymphatic Sac Tumors

These histologically benign tumors originate in the vestibular aqueduct and grow locally invasive into the petrous bone. Patients will typically present with hypoakusis or hearing loss (100%), tinnitus (77%), dysequilibrium (62%), and facial paresis (8%).[75] Tumor-associated intralabyrinthine hemorrhage may lead to acute hearing loss and vestibulopathy due to endolymphatic hydrops.[76] All patients with endolymphatic sac tumors (ELSTs) should undergo diagnostic testing for VHL mutations since endolymphatic sac tumors can be the first manifestation of VHL disease.

In general, early surgical resection is recommended to enhance the possibility of complete resection and avoid hearing loss or vestibular symptoms, which may be irreversible.[77] The timing of surgery depends on the severity of symptoms, the slow but variable growth of the tumors, the possibility of injury to the 7th and 8th cranial nerves and possible bilateral occurrence. The role of radiation in the treatment of these tumors remains controversial.[78] Description of pharmacological therapies is scarce and is discussed in the section on targeted therapy.

Renal Manifestations

Patients with VHL disease may develop renal cysts and renal cell carcinomas (RCCs).[46,79–83] VHL-disease-associated RCCs tend to be low grade and minimally invasive,[84] their rate of growth varies widely.[85,86] VHL alterations are also observed in 60–70% of sporadic RCCs.[87]

The goal of therapy is the prevention of metastasis and maintenance of kidney function. Most authors recommend nephron-sparing surgery for carcinomas that exceed 3 cm in size.[79,88] Other authors suggest that a diameter of 4 cm is also acceptable.[89] The "3 cm rule" takes into account the overall survival and quality of life (considering potential premature renal failure and need for dialysis).

Although the gold standard for treating renal tumors is open and minimally invasive partial nephrectomy, alternative therapies including cryotherapy and radiofrequency ablation are also presently utilized.[90] Pharmacological therapy is used for metastatic disease and is discussed in the section on targeted therapy.

Pheochromocytoma

In more than 33% of patients, pheochromocytomas can occur in a familial syndrome such as the VHL syndrome.[91,92] The presence of pheochromocytomas defines VHL disease type 2 (A,B,C). More than 26% of VHL patients developed pheochromocytomas in major series.[93–96]

Few tumors are hormonally inactive with plasma-free metanephrine levels within the normal reference range. The tumors occur bilaterally in up to 39% of patients.[93] The tumors can also be found in the sympathetic chain and are then mostly unable to produce and secrete catecholamines.[92,97–100] In general, extra-adrenal pheochromocytomas have a higher frequency and potential of malignancy than pheochromocytomas located in the adrenal gland.[101] No biomarkers are available that can reliably distinguish a benign from a metastatic pheochromocytoma.

Screening for pheochromocytoma includes measurements of urinary catecholamine metabolites and fractionated metanephrines, as well as of plasma-free metanephrines.[94,102,103] The diagnosis can further be established by abdominal computed tomography and/or magnetic resonance imaging.[58,105] Given the low frequency of extra-adrenal pheochromocytomas (15%) or metastatic (<5%) pheochromocytomas in patients with VHL disease, selected patients should undergo 123I-MIBG scanning to screen for extra-adrenal or metastatic disease[18,101,105] F-FDG, and more recently,[67] Ga DOTATATE PET have been shown to offer better test characteristics for assessment and staging of pheochromocytoma/paraganglioma than [106] MIBG scintigraphy[107–110] The detection of a pheochromocytoma in patients with VHL syndrome is important to prevent life-threatening hypertensive attacks. Hormonally active pheochromocytomas should generally be treated before surgical treatment of other VHL lesions to prevent intraoperative hypertensive complications and require perioperative blockade.[111]

It is recommended that pheochromocytoma screening should be started already in childhood at the age of 4 years,[58,92,94,96,112] acknowledging that metastatic pheochromocytoma occurs in asymptomatic VHL patients.[113]

In patients with apparently familial pheochromocytoma there is a 50% chance of VHL disease, whereas the disease is detected in only 10% of patients with sporadic pheochromocytoma.[92,114,115] More than 70% of pediatric pheochromocytomas are VHL related.

Treatment of nonmetastatic adrenal pheochromocytoma consists of adrenal cortical sparing (partial) tumor removal, whenever possible.[116–119] Minimally invasive adrenal sparing removal of the pheochromocytoma should be performed in most if not all patients.[120]

This potentially impacts survival as the risk of death from primary adrenal insufficiency may be higher than dying of a recurrent pheochromocytoma. Metastatic pheochromocytoma occurred in 3 patients of a VHL cohort consisting of 273 patients[94] and recurrences occurred in 8 of the 273 patients. Bausch and colleagues found a 38% risk of developing a second paraganglioma in pediatric patients diagnosed with pheochromocytoma.[121]

There is no consensus on whether hormonally inactive pheochromocytomas require treatment. The decision will depend on tumor growth, symptoms, and possible metastasis.[106,122] Mutation-adjusted surveillance aims to increase life expectancy.[123]

Epididymal Cystadenoma

About 50% of male VHL patients develop these non-malignant tumors.[124] Epididymal cystadenomas typically arise in the head of the epididymis and contain cystic as well as adenomatous areas and. These lesions are usually asymptomatic. Malignant transformation has not been reported. Obstruction of efferent ductules and spermatic cords may result in fertility problems in rare cases. If necessary, these tumors can be seen on ultrasound.

The female counterparts are cystadenomas of the broad ligaments. They play no major clinical role. "Adnexal papillary cystadenoma" are rare, but may require surgery. They are of probable mesonephric origin.

Pancreatic Manifestations

Pancreatic manifestations in VHL disease include cystadenomas, cysts and pancreatic neuroendocrine tumors.[125] A recent series of 48 patients with VHL disease at the Mayo Clinic also revealed 5 patients with branch duct intraductal papillary neoplasm.[126]

Pancreatic manifestations are observed in 35–70% of VHL patients.[55,127,128] It may be difficult to differentiate between benign microcystic adenoma and a pancreatic neuroendocrine tumor. Pancreatic neuroendocrine tumors also reveal a staggering growth pattern similar to hemangioblastoma.[129]

Besides rare cases of bile duct obstruction or pancreatic insufficiency these tumors are usually asymptomatic. Screening is performed by contrast-enhanced MRI with. Image acquisition has to be performed in the early arterial phase. Pancreatic neuroendocrine tumors are usually solid lesions, whereas microcystic adenomas reveal a multicystic appearance. Microcystic adenomas usually need no treatment, whereas pancreatic neuroendocrine tumors need to be considered for surgery. Mutations in exon 3, especially of codons 161/167 are at enhanced risk for metastatic pancreatic neuroendocrine tumors.[130] Most

of these lesions are small and slow-growing. In general, VHL-associated pancreatic neuroendocrine tumors have a favorable prognosis compared to sporadic tumors.[131] Tumors with a diameter over 2.8 cm should be treated surgically to avoid metastasis according to a recent multi-center study.[130] 68Ga-DOTATOC PET/CT has better sensitivity in detecting pancreatic NET (size range 4–38 mm) in patients with VHL than 111In-octreoscan.[132]

Resection of pancreatic tumors may be combined with laparotomy for other VHL associated lesions.[133,134] Biliary obstruction with pancreatic insufficiency can be treated by placing biliary stents or replacing pancreatic enzymes. A new option is organ-sparing minimally invasive resection which can be applied to tumors in the tail and the body of the pancreas.[135] Chemotherapy is currently under investigation and discussed in the section on targeted therapy.

VHL Screening and Prognosis

A careful family history and screening for other lesions associated with VHL should be performed in all patients with hemangioblastoma, the index tumor of VHL disease. Genetic testing for VHL disease is recommended for all patients with hemangioblastoma.[136,137]

If a diagnosis of VHL disease is established, patients should undergo an annual screening program (Box 1) for the timely identification of manifestations before irreversible deficits or metastasis occurs. Screening includes periodic contrast-enhanced MRI scans. While CNS gadolinium accumulation will eventually occur in virtually all VHL patients, no pathological effect of this accumulation is known so far.[138]

The screening programs vary slightly between different centers. A typical program is presented in Box 1. The screening includes several contrast MRI scans. Most centers perform three different scans. Brain, spine and abdomen. Since the discovery of Gadolinium (Gd) depositions in the CNS it is being considered to minimize the use of Gadolinium. These depositions are particularly frequent in VHL patients.[138] A shortened 35-mins whole-body MRI protocol with only one Gd injection has been recently suggested[139] making VHL screening also quicker and more convenient for patients.

The overall life expectancy of VHL patients used to be limited with a median survival of around 50 years.[2,60] However, the introduction of clinical screening enabled timely diagnosis and prophylactic treatment of VHL lesions leading to significantly improved life expectancy.[140] Modern management of VHL disease-associated lesions has achieved a life expectancy of additional 10 years.[141]

Biomarkers in VHL Disease

Timely screening for and preventive treatment of lesions is key to the successful management of VHL patients. Recent developments in oncology are biomarkers including tumor markers, disease activity markers, liquid biopsy and others. We here review the knowledge of systemic biomarkers. Tumor-specific markers, which are detected within the tumor tissue, are not reviewed here. To date, systemic biomarkers do not play a role in the clinical practice of VHL disease, except for plasma and urinary catecholamine metabolites and fractionated metanephrines for pheochromocytoma. However, there are interesting new developments. Certain markers or combinations of markers may be further developed for clinical use in the future and may supplement or even replace other time-consuming screening examinations.

Measuring plasma levels of HIF-dependent molecules appears to be an obvious attempt to monitor disease activity in VHL patients. One group has suggested using plasma VEGF and miRNA210, a hypoxia-inducible micro-RNA, to monitor disease activity in VHL patients with retinal hemangioblastomas. They report that levels of both molecules decreased in all patients under therapy with propranolol.[142] Other groups have observed a decrease of serum levels of the HIF-dependent proteins VEGF and also the receptors VEGFR-2 and VEGFR-3 as well as CA9 during therapy with sunitinib and sorafenib in patients with VHL-associated and sporadic RCC.[143] Reduction of serum VEGF levels was also detected in mice with xenografted VHL RCCs under propranolol treatment.[144]

Also, monitoring tumor secretion products may be of interest in VHL disease. VHL patients with pancreatic neuroendocrine tumors had a correlation with plasma vasoactive intestinal peptide and pancreatic polypeptide levels in one study.[145]

The significance of VHL mutations as a predictive marker in sporadic RCCs is well described. VHL mutations in circulating tumor DNA have been detected by liquid biopsy using a Taqman assay.[146]

Another study describes the identification of VHL mutations in circulating cancer cells with single-cell genetic analysis.[147]

Polyglobulia has been described as a paraneoplastic phenomenon in VHL disease. It was reported to occur in CNS

hemangioblastomas as a consequence of the secretion of erythropoietin. More recent studies show that this phenomenon is rare, but if present, polyglobulia subsides with the removal of the hemangioblastoma.[69] This is consistent with reports of erythropoietic activity in a subset of hemangioblastomas.[37] Interestingly, the level of serum erythropoietin and the extent of polyglobulia do not correlate.[148] However, the size of the solid tumor component correlates with polyglobulia. Therefore, polyglobulia is a biomarker for tumor growth in a subset of hemangioblastomas. Polycythemia has also been reported in patients with VHL disease and renal cancer[149] and pheochromocytoma.[150]

In general, the knowledge on biomarkers in VHL disease is scarce and this should be addressed in future clinical studies on VHL disease.

Targeted Therapy in VHL Disease

Targeted cancer therapy aims to block specific molecular pathways of cancer cells. Targeted drugs can be subdivided into compounds that inhibit the growth of the primary tumor, prevent invasion in nearby tissue; or drugs that block angiogenesis, metastasis and consequent development of secondary tumors. Because most VHL related tumors are benign, or only carry a low rate of metastasis, targeted VHL therapy mainly focuses on inhibiting primary tumor growth and angiogenesis.

Up to date, the incomplete understanding of VHL tumorigenesis has thwarted the development of a targeted therapy against the disease. Furthermore, VHL tumors are known for their saltatory growth pattern with quiescent phases, which complicates the distinction between response to treatment and natural behavior. Considerable effort has been spent on pharmacological trials, harvesting mixed results. There are no systematic reviews on pharmacological trials in VHL disease. We have reviewed more than 50 studies or case reports and summarized the findings here. The studies are categorized by the main action of their respective drug (Figure 6).

Monoclonal Antibodies

Because VHL tumor vascularization (and consequently also tumor growth) is largely dependent on VEGF, many VHL treatment trials have focused on blocking the VEGF-pathway.

Intravitreal injection of anti-VEGF monoclonal antibodies has been widely used as therapy for neovascular age-related macular degeneration. It is now being repurposed for retinal hemangioblastomas in VHL disease.[151]

Bevacizumab is a monoclonal antibody that prevents interaction between VEGF-A (isoforms 206, 189, 165, 121
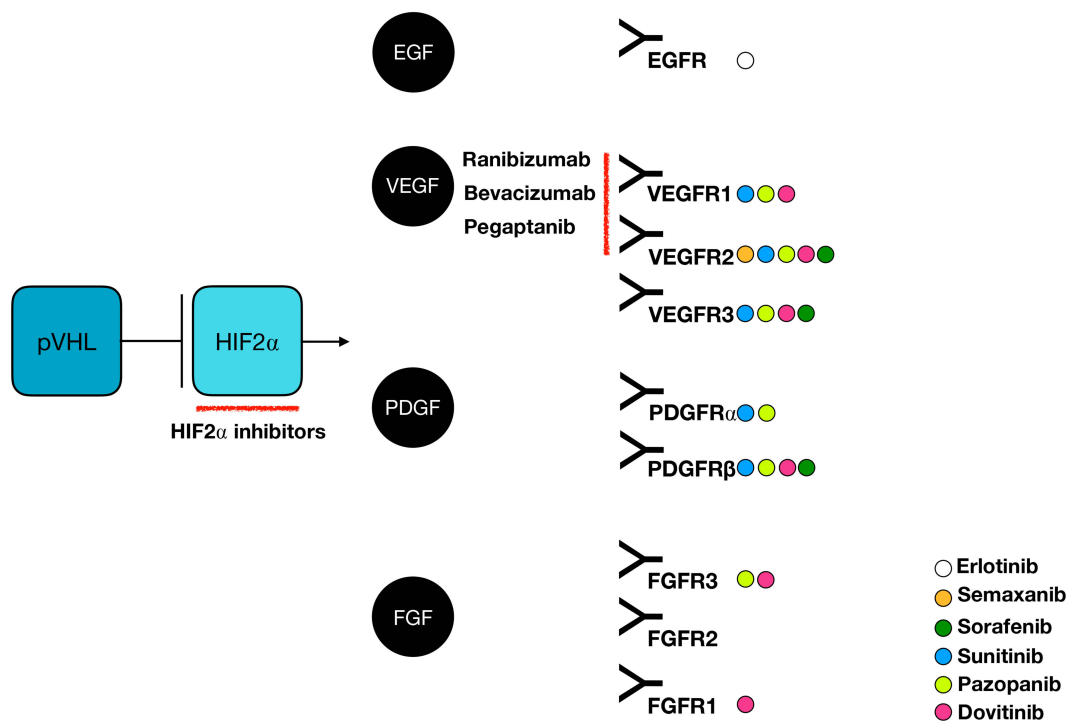

Figure 6 Molecular targeting in VHL disease: action mechanisms. **Abbreviations:** EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; HIF, hypoxia-inducible factor; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

and 110) and its receptors (VEGFR1/2). Research groups have reported moderate effects of intravitreal bevacizumab on retinal hemangioblastomas.

Ach et al reported a VHL patient who experienced growth stabilization of retinal hemangioblastomas after several years of intravitreal bevacizumab injections.[152]

Tano et al treated two VHL patients with intravitreal bevacizumab in combination with vitrectomy, to stabilize a proliferative vitreoretinopathy caused by retinal hemangioblastomas. Even though exudation was suppressed, hemangioblastoma volumes remained stable.[153] Hrisomalos et al reported a similar response in one VHL patient, after a regimen of 12 bevacizumab injections over 60 months.[154] Tsai et al published contradictory results: photodynamic therapy in combination with intravitreal bevacizumab and corticosteroids reduced the volume of multiple retinal hemangioblastomas in one VHL patient, but exudation was not affected. According to Tsai et al, corticosteroids seem to be more effective in reducing exudation than bevacizumab.[155] Walker et al described a VHL patient with rebound neovascularization after intravitreal bevacizumab injection, again without effect on tumor volume.[156]

Also, the systemic use of bevacizumab has been tested. Wackernagel et al reported the active development of retinal hemangioblastomas during systemic bevacizumab treatment in a VHL patient. Side effects of systemic use were paresthesias and nail petechiae.[157]

To conclude; laser photocoagulation, cryotherapy, photodynamic therapy and pars plana vitrectomy seem to remain the gold standard for the treatment of retinal VHL hemangioblastomas. Bevacizumab may be considered as adjunctive therapy to stabilize exudation caused by multiple treatments, and to halt neovascularization.

Ranibizumab is another monoclonal antibody that prevents interaction between VEGF-A (isoforms 165, 121, 110 and theoretically 206 and 189) and its receptors (VEGFR1/2). After three intravitreal ranibizumab injections, Michels et al saw stabilization and decreased exudation of a retinal hemangioblastoma in a VHL patient.[158] Wong et al conducted a prospective case series including 5 VHL patients with advanced retinal hemangioblastomas, who followed a 24-week regimen of 7 intravitreal ranibizumab injections. Three subjects noticed transient vision improvement, which was however followed by progressive tumor growth and macular exudation. In one patient, macular exudate even increased immediately. One patient experienced prolonged vision improvement and a decrease of macular exudate after 10 injections, with stabilization of tumor volume.[159]

Pegaptanib is a monoclonal antibody that selectively binds the VEGF-A 165 isoform (which is most predominant in hemangioblastomas) and thereby prevents interaction with its receptors (VEGFR1/2). Dahr et al published a pilot case series including 5 VHL patients with retinal hemangioblastomas that were ineligible for conventional treatment. After six intravitreal pegaptanib injections, macular exudation decreased in two patients, and one of them experienced improved visual acuity. Three patients had adverse events that necessitated treatment withdrawal; such as retinal detachment after laser treatment, retinal detachment caused by exudation, and progressive macular edema. Pegaptanib did not reduce retinal hemangioblastoma volumes and was therefore considered as a palliative treatment modality only.[160]

We conclude that monoclonal antibodies directed against VEGF are mainly applied as adjunctive treatment to reduce macular exudation; in VHL patients with advanced juxtapapillary or peripheral retinal hemangioblastomas, which are ineligible for conventional treatment. However, because of mixed results, larger prospective randomized trials may be needed to evaluate their efficacy and safety.

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors are targeted drugs that block cellular signal transduction cascades. As for monoclonal antibodies, pharmacologic VHL trials have mainly focused on the VEGF tumor pathway.

Semaxanib (SU5416) is a small molecule tyrosine kinase inhibitor of VEGFR2 and stem cell factor receptor c-kit. It has been widely used as a chemotherapeutic for liver metastases of colon cancer and other malignancies. To date semaxanib is not licensed for human use outside clinical trials. Its application in VHL disease has been tested in case reports and small series.

In 2002, Aiello et al reported a VHL patient with an optic nerve head hemangioblastoma, who was treated with 10 cycles of systemic semaxanib. Fundoscopic findings did not change; however, a positive correlation was found between semaxinib dose and visual acuity. Interestingly, Aiello et al reported no change in tumor volumes of the patient's synchronous cerebellar, spinal and pancreatic lesions.[161]

Later, other semaxanib trials have followed. Richard et al conducted a toxicity assessment study on 3 VHL patients. Semaxanib caused secondary polycythemia, without effect on hemangioblastoma volumes.[162]

Girmens et al reported the decrease in macular exudate around a retinal hemangioblastoma, in a VHL patient who

was treated with semaxanib for 7 months. However, volume and vision remained stable.[163]

In 2004, Madhusudan et al conducted a Phase I/Phase II study with 4-week cycles of 8 semaxanib injections, including 6 VHL patients. In one patient, brain/spinal hemangioblastomas and pancreatic cyst volumes remained stable after 22.4 months of ongoing treatment and after 41.4 months of follow-up. However, upper motor neuron symptoms decreased. Another patient with retinal/brain/spinal hemangioblastomas and renal/pancreatic/epididymal cysts only experienced complete regression of a sole retinal lesion (which was also treated with laser coagulation). The patient had improved strength and sexual function after 10 months of treatment. Tumor volumes remained stable on imaging. Clinical response in the other four patients was not described.[164]

A similar improvement of upper motor neuron symptoms caused by semaxanib, without effect on tumor volume, was described by Schuch et al in a VHL patient with multiple spinal hemangioblastomas.[165]

To our great interest, Jennens et al reported a VHL patient with the complete metabolic and radiologic response of a metastatic renal cell carcinoma, after 11 systemic semaxanib injections.[166]

Sunitinib is a first-generation tyrosine kinase inhibitor of multiple receptors (including VEGFR1/2/3, and PDGFR αand β). It is by far the most investigated targeted therapy in VHL disease. However, side effects often lead to disruption of treatment: fatigue, nausea, vomiting, diarrhea, mucositis, hematologic disturbances, nausea, hypertension and hand-foot neuropathy.[167–179]

Jimenez et al used oral sunitinib to treat a VHL patient with a metastatic pelvic pheochromocytoma (positively staining for VEGF and PDGF beta on immunohistochemistry). The pheochromocytoma started shrinking after 6 months. Interestingly, also the patient's renal (staining positive for VEGF) and pancreatic tumor volumes decreased.[167]

Other researchers published similar results in VHL patients undergoing several years of sunitinib treatment: Ali et al (1 patient),[169] Wang et al (1 patient),[170] Kobayashi et al (1 patient),[172] Oudard et al (6 patients),[173] Kim et al (4 patients),[174] Yuan et al (3 patients),[176] Tsimafeyeu et al (1 patient),[178] Babinska et al (1 patient)[179] and Nuñez et al (3 patients).[177] Results range from disease stability to partial response in (metastatic) renal cell carcinomas, in some (metastatic) pancreatic neuroendocrine tumors and in one pheochromocytoma.

Tsimafeyeu et al describe complete regression of a metastatic renal cell carcinoma in a VHL patient, after 11 months of sunitinib treatment.[178]

Jonasch et al conducted a major pilot trial, treating 15 VHL patients with sunitinib. After four cycles, response was absent in hemangioblastomas and partial in 33% of renal cell carcinomas. Rebound growth in both tumor groups occurred after 48 months. According to Jonasch et al, the higher concentrations of VEGFR2 in renal cell carcinomas compared to hemangioblastomas may explain differences in treatment sensitivity. Pancreatic NETs and cysts, retinal hemangioblastomas and renal cysts remained stable. Two patients with retinal hemangioblastomas experienced increased ocular discomfort, a finding also reported by Oudard.[168,173]

In a retrospective analysis of 14 VHL patients, Roma et al reported partial response to sunitinib in 64% of different VHL tumors (progressive renal cell carcinomas; and pancreatic, adrenal and ovarian lesions), yielding a progression-free survival of 71.4% after 2 years. Hemangioblastomas remained stable.[171]

In conclusion, sunitinib response seems to be dependent on several individual patient characteristics; such as overall VHL disease severity, performance status, age and tumor VEGFR status. Sunitinib is mainly used as a palliative treatment modality for temporary symptom control of renal cell carcinomas and pancreatic neuroendocrine tumors. Complete remission of renal cell carcinomas has been described. Sunitinib does not seem to affect cerebellar and retinal hemangioblastomas. Transient shrinking of medullary hemangioblastomas, with neurologic symptom improvement, was described by Oudard.[173]

Similar to sunitinib, pazopanib is a first-generation inhibitor of multiple tyrosine kinases (including VEGFR 1/2/3; FGFR3 and PDGFR αand β). It has been approved for the treatment of advanced renal cell cancer and advanced soft tissue sarcoma.

In 2012, Kim et al reported a VHL patient with multifocal renal cell carcinoma and multiple cerebellar hemangioblastomas that were all progressive under sunitinib treatment. Subsequent pazopanib treatment improved bulbar symptoms and ambulation. On imaging, cerebellar hemangioblastoma volume decreased, and renal cell carcinoma growth rate slowed.[180]

Also remarkable is the report of Migliorini et al in 2015, about a tetraplegic VHL patient with a non-resectable spinal hemangioblastoma, who regained

ambulation after pazopanib treatment. The tumor seemed to be reshaped on MRI.[181]

Taylor et al described a VHL patient with the radiologic shrinking of two spinal hemangioblastomas, after pazopanib treatment. Neurologic symptoms did not change, nor did the tumor volume of other hemangioblastomas and one renal cell carcinoma.[182]

In 2018, Jonasch et al conducted a single-arm nonrandomized phase II study with pazopanib on 30 VHL patients. After a median follow-up of 12 months, the radiologic objective response rate was 52% in renal cell carcinomas (59 tumors; 2 complete responses, 29 partial responses, 28 stable diseases), 53% in pancreatic serous cystadenomas (17 tumors; no complete responses, 9 partial responses, 8 stable diseases), and 4% in central nervous system hemangioblastomas (49 tumors; no complete responses, 2 partial responses, 47 stable diseases, 2 patients with intratumoral hemorrhage). None of the 30 patients developed new VHL related lesions or progressive disease during pazopanib treatment. Interestingly, the type of VHL mutation did not correlate with disease response.[183]

Finally, Salim described the 9-month stability of a VHL patient with retinal hemangioblastomas treated with pazopanib[184].

Reported side effects of pazopanib are fatigue, diarrhea, increase of transaminases, oral mucositis, neutropenia, alopecia/hair depigmentation, hypertension, gastritis and appendicitis.[180,181,183]

In conclusion, pazopanib seems to have a larger therapeutic effect on renal cell carcinomas, compared to sunitinib. However, study results are inconsistent and side effects are not to be neglected.

Erlotinib is a tyrosine kinase inhibitor of EGFR, indicated for the treatment of metastatic non-small cell lung carcinoma and metastatic pancreatic cancer. In 2001, Rogers et al reported progressive disease under oral erlotinib in a young VHL patient with multiple cerebellar and spinal hemangioblastomas.[185]

Dovitinib is a tyrosine kinase inhibitor of multiple receptors (including VEGFR1/2/3, PDGFRβ and FGFR1/3). It is currently under investigation for refractory multiple myeloma and metastatic renal cell carcinoma. In 2018, Pilié et al conducted a pilot study of dovitinib in 6 VHL patients. All patients discontinued treatment due to noncompliance or side effects (fatigue, vomiting, severe rash, transaminitis, neutropenia, mucositis and dyspnea). The

best response was a stable disease of central nervous system hemangioblastomas.[186]

Sorafenib is a multiple tyrosine kinase inhibitor of VEGFR2/3 and PDGFR β, among other receptors. In 2017, Choi et al report partial response to sorafenib of multiple small renal cell carcinomas and pancreatic cysts in 2 VHL patients. Retinal and spinal hemangioblastomas did not respond. Manageable diarrhea was reported as a side effect.[187]

Biological Response Modifiers

Biological response modifiers are drugs that boost or modulate the host's autologous immune response to neoplasia. Some of these modifiers have been tested in vitro and in small VHL patient groups: roquinimex, thalidomide, IFN-α-2a, HIF2α inhibitors, octreotide, clarithromycin and immunotherapy.

Roquinimex is a derivative quinoline that exerts its anti-neoplastic potential by blocking angiogenesis and decreasing TNF-alpha synthesis. Second, by stimulating NK cell and macrophage activity, it also has immunostimulant properties. In 1999, roquinimex caused a shrinking of von-Hippel-Lindau paraganglioma xenografts in mice.[188] No further studies have followed.

Thalidomide acts as an immunosuppressive and anti-angiogenic agent, by modulating the actions of several cytokines. It was withdrawn from the market due to its teratogenic side effects. However, in 2004, Tan et al used thalidomide together with rofecoxib to control post-radiation inflammatory reaction in a VHL patient with a cerebral hemangioblastoma.[189] In 2009, Sardi et al describe the growth stabilization of two progressive spinal hemangioblastomas, in a VHL patient treated with thalidomide during a follow-up period of 37 months.[190]

IFN-α-2a binds to type 1 interferon receptors. It has been previously applied as an antiviral agent in chronic hepatitis C and as an antineoplastic agent in several types of leukemia. In 2011, Niemela et al treated 3 VHL patients with recombinant IFN-α-2a. They reported no significant shrinking of retinal, cerebellar nor spinal hemangioblastomas. Also, pancreatic and renal cysts remained stable. A mild diminishment of blood flow was noticed in retinal hemangioblastomas, potentially by inhibiting VEGF secretion.[191]

Following VHL inactivation, HIF2α is constitutively upregulated in sporadic and VHL-associated renal cell carcinomas, stimulating tumor growth by activating multiple downstream targets such as VEGF, PDGF, EGFR,

TGFα, FGF, GLUT1, Epo, NO-synthase and cyclin D. Therefore, a strong rationale exists for directly inhibiting HIF2α, instead of VEGF alone.

In 2015, Metelo et al reported that pharmacological HIF2α mRNA inhibition in zebrafish improved VHL phenotype (decreasing erythrocytosis and blood vessel formation in the retina, brain, liver and kidney). Further preclinical pharmacologic moderations are needed before its implementation in clinical studies.[192] A remaining question is whether HIF2α inhibitors also influence VHL-associated hemangioblastomas, or (extra-adrenal) paragangliomas, which can be either HIF-driven or non-HIF driven.[193]

In 2017, Sizdahkhani et al demonstrated the presence of somatostatin receptors (1, 2a, 4 and 5) in VHL related hemangioblastomas. They discovered apoptosis of cultured VHL hemangioblastoma cells that were treated with the somatostatin analogue octreotide. Octreotide also caused volume and symptom reduction of an inoperable suprasellar hemangioblastoma in one VHL patient.[194]

Also in 2017, O'toole et al used octreotide in a VHL patient with multiple pancreatic neuroendocrine tumors, yielding partial response in all tumors.[195]

Yaghobi Joybari et al reported that octreotide/everolimus caused symptom improvement in a VHL patient with a metastatic pancreatic neuroendocrine carcinoma. Radiological follow-up data were not available.[196]

Clarithromycin, an antibiotic, has been repurposed as an anti-cancer agent. By modulating cytokine biology and VEGF expression, it has inhibitory effects on inflammation and angiogenesis. In 2019, Ma et al used clarithromycin to treat a VHL patient with a progressive ELST tumor. After 3 months, the ELST tumor remained stable on CT imaging. Pancreatic and renal lesions shrunk or remained stable. Some renal lesions showed progressive growth. No side-effects were observed.[197]

Only little data are available on immunotherapy in VHL disease. In 1993, Weidmann et al established in vitro sensitization of lymphocytes to autologous renal cell carcinoma tumor cells in two VHL patients. Combined with the injection of interleukin-2, the sensitized lymphocytes caused volume reduction of pulmonary metastasis, without affecting renal cell carcinoma volume.[198]

Miscellaneous

Based on its previous success rates with infantile hemangiomas, in 2015 Albiñana et al investigated the effect of propranolol on hemangioblastomas in VHL disease. Acting as a nonselective β1 and β2-adrenergic antagonist, propranolol caused apoptosis and inhibition of downstream HIF targets in hemangioblastoma cell cultures (such as VEGF and FGF). However, its exact mechanism of action was unknown.[199] Two years later, the same research group used propranolol to treat 7 VHL patients with retinal hemangioblastomas. There was no effect on tumor volume. Resorption of tumor exudate was seen in two patients.[142] Another two years later, Albiñana et al applied a highly specific β2-adrenergic receptor blocker (ICI-118,551), which exhibited similar effects on hemangioblastoma cells in vitro.[200]

In 2018, Shepard et al conducted a similar experiment with propranolol on in vitro VHL hemangioblastoma and renal cell carcinoma cells. Both tumor cell types responded with signs of apoptosis. Propranolol also reduced tumor volume of renal cell carcinoma xenografts in mice. Afterwards, Shepard et al retrospectively analyzed the effect of propranolol on 66 hemangioblastomas in 3 VHL patients who used to receive propranolol for other clinical reasons. Median growth rate of hemangioblastomas was reduced, but did not stop, during a 2.1-year median follow-up.[144]

Up to date, there are no reports on alkylating agents nor antimetabolites used in VHL patients. However, VHL mutation status is an important predictor for response to alkylating agents in sporadic renal cell carcinomas.[201]

Halofuginone, a plant derivate, decreases gene expression of collagen type 1 and matrix metalloproteinases; thereby thwarting VEGF-regulated angiogenesis. In 2003, Gross et al discovered that halofuginone led to angiogenic inhibition of a VHL pheochromocytoma xenograft in mice. There was no tumor regression. The authors suggested the future investigation of its applicability as a chemotherapeutic in the early stages of highly vascular VHL tumors.[202]

Little is known about radiopharmacological treatment. In 1995, Pujol et al report near-complete regression of a metastatic pheochromocytoma in a VHL patient treated with Iodine-131 metaiodobenzylguanidine ([131I] MIBG).[203]

Conclusion

Even though randomized prospective trials are needed, intravitreal bevacizumab injections may be considered for refractory and exudative retinal hemangioblastomas. The effects and safety profile of ranibizumab and pegaptanib are less well studied, neither are the effects of bevacizumab on other VHL-related tumors.

Regarding monoclonal antibodies, larger randomized trials including control groups are needed to differentiate therapeutic stabilization from natural tumor behavior. Semaxanib causes symptomatic improvement in some central nervous system hemangioblastomas, without affecting tumor volume. We believe that the same temporary relief may be expected from corticosteroids. The effects of sunitinib and pazopanib are potentially depending on different factors such as VEGFR activity, and range from disease stability to partial response in (metastatic) renal cell carcinomas and (metastatic) pancreatic neuroendocrine tumors. Complete regression of one metastatic renal cell carcinoma has been described for both semaxanib and sunitinib. The effect of pazopanib on renal cell carcinomas seems slightly greater. Sunitinib causes disease stability to partial response in some pheochromocytomas. Sunitinib and pazopanib do not seem to affect hemangioblastoma tumor volumes, but some patients experienced symptomatic improvement after treatment with pazopanib. Sunitinib and pazopanib have severe side effects.

The in vitro effect of propranolol on hemangioblastoma and renal cell carcinoma cell cultures seems promising. Again, larger randomized trials including control groups are needed to differentiate therapeutic stabilization due to propranolol, from natural tumor behavior.

Agents such as sorafenib, thalidomide, HIF2α, octreotide and immunotherapy may seem promising, but more preclinical and larger patient studies are needed to assess their efficacy and safety profile.

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Author Contributions

All authors contributed to literature analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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