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Advancements in understanding the molecular mechanisms and clinical implications of Von Hippel-Lindau syndrome: A comprehensive review

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ABSTRACT

Von Hippel-Lindau Syndrome (VHL) is a rare genetic disorder characterized by tumors in multiple organs, including the kidneys, pancreas, and central nervous system. This comprehensive review discusses the genetic basis and clinical manifestations of VHL, as well as recent advancements in understanding the molecular mechanisms that lead to tumor formation. The authors highlight the role of hypoxia-inducible factors and the ubiquitin-proteasome system in VHL-associated cancer development .The review also discusses the potential clinical implications of these findings, such as the development of targeted therapies for VHL-associated cancers. However, the authors note the challenges associated with developing effective treatments for this complex disease, including limited patient availability for clinical trials due to its rarity .Overall, this review provides valuable insights into our current understanding of VHL and offers important avenues for future research aimed at improving the diagnosis, treatment, and management of VHL patients. By illuminating the molecular underpinnings of VHL-associated cancers, this work may ultimately help to develop more effective treatments and improve outcomes for patients with this challenging disease.

Introduction

Von Hippel-Lindau (VHL) disease is a rare genetic disorder that affects approximately 1 in 36,000 individuals worldwide [1,2]. It is caused by mutations in the VHL gene, which is located on 3p25-26. The VHL gene is responsible for encoding a protein called pVHL, which plays a critical role in regulating cellular metabolism, angiogenesis, and apoptosis.

In general, patients with VHL syndrome usually manifest symptoms at various ages, depending on the specific manifestations of the disease. The age of onset can range from childhood to adulthood. As for a cure, there is currently no known cure for VHL syndrome. However, with adequate treatment, the progression of the disease can be managed, and complications can be minimized. Unfortunately, some patients with VHL syndrome may die from complications related to the disease, especially if the tumors become malignant or if they affect critical organs. The survival rate of individuals with VHL syndrome can vary depending on the specific genetic mutation and the extent of tumor involvement. To monitor and detect potential tumors or complications early, regular surveillance protocols are recommended for individuals with VHL syndrome. These protocols typically involve periodic imaging studies such as magnetic resonance imaging (MRI) or computed tomography (CT) scans. The frequency and type of surveillance may vary depending on the individual's specific situation and the recommendations of their healthcare provider.

VHL disease is characterized by the development of multiple benign and malignant tumors throughout the body, including hemangioblastomas, renal cell carcinomas, pheochromocytomas, and pancreatic neuroendocrine tumors [3,4]. The tumors can occur at any age, but are most commonly diagnosed in young adults. The clinical manifestations of VHL disease can vary widely depending on the individual, and can include headaches, vision loss, hearing loss, high blood pressure, abdominal pain, and palpitations [5]. The specific symptoms and severity of the disease can also vary depending on the type and location of the tumors (Fig. 1).

VHL disease is inherited in an autosomal dominant pattern, meaning that an individual only needs to inherit one copy of the defective VHL gene from one parent to develop the disease. Those with VHL disease have a 50% chance of passing it on to their offspring [6]. This rare genetic disorder predisposes individuals to the development of multiple

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benign and malignant tumors throughout the body due to mutations in the VHL gene. As a result, it can lead to a wide range of clinical manifestations. Early diagnosis and management of VHL disease are crucial for improving patient outcomes and reducing the risk of complications. In this review, we summarize the comprehensive discussion of the genetic basis, clinical manifestations, and recent advances in molecular mechanisms of VHL syndrome. This is highly beneficial for clinical physicians in relevant disciplines, researchers interested in this disease, and individuals with potential genetic risks to understand the full spectrum of this condition.

The methodology for identifying relevant studies

In this comprehensive review, we employed a systematic search strategy to identify relevant studies. Multiple electronic databases, such as PubMed, Scopus, and Web of Science, were searched using a combination of keywords including VHL gene, HIF, VHL disease, and the treatment of VHL syndrome, and subject headings related to the topic under investigation . The time frame of the literature search was clearly defined to reflect the most current evidence available. We searched articles published from 1990 to 2023, considering studies within this time frame to maintain the relevance and currency of the review. During the selection process, we carefully screened the identified studies based on predefined inclusion and exclusion criteria. Any studies that did not meet the inclusion criteria were excluded from the review. The reasons for exclusion may include factors such as inappropriate study design, irrelevant outcomes, or insufficient data.

The function of the VHL gene and its encoded protein pVHL

The VHL gene is located on chromosome 3p25-26 and encodes a tumor suppressor protein called pVHL. The gene consists of 854 nucleotides including three exons that span over 11 kilobases of DNA [7] (Fig. 2). A splice variant without exon 2 has been identified, however, it is thought to lack tumor suppression activity [8]. The pVHL protein has two isoforms, pVHL30 and pVHL19, resulting from alternative start codons. Both isoforms possess similar characteristics and exhibit tumor-suppressor activity in vivo. pVHL30 consists of 213 amino acids with a molecular weight of 30 kDa, while pVHL19 lacks a 53-amino acid N-terminal pentameric acid repeat domain and predominates in many tissues, consisting of 160 amino acids with a molecular weight of 19 kDa [9,10]. The term pVHL is commonly used to describe both proteins. The structure of pVHL protein mainly comprises three functional domains: the β-sheet domain at the N-terminus for substrate binding, the α-helical domain in the middle, and the β-sheet domain at the C-terminus for dimerization and binding with Elongin C/Elongin B [11]. Although pVHL shuttles between the nucleus and cytoplasm, the majority of this protein is located in the cytoplasm under steady-state conditions [12]. Furthermore, a portion of pVHL can be detected in mitochondria and associated with the endoplasmic reticulum [13]. In recent years, numerous studies have shown that the expression and function of several genes involved in tumorigenesis are regulated by the VHL protein [14].

1. Hypoxia-inducible factor (HIF) genes: Von Hippel-Lindau (VHL) protein is an E3 ubiquitin ligase that plays a key role in the degradation of hypoxia-inducible factor-1 (HIF-1). HIF-1 is a transcription factor that regulates the cellular response to hypoxia, or low oxygen levels. Under normoxic conditions, VHL recognizes and binds to hydroxylated proline residues in the oxygen-dependent degradation domain (ODD) of HIF-1α, which is then ubiquitinated by a complex of VHL, Elongin B/C, and Cullin-2 (Fig. 3). The polyubiquitinated HIF-1α is then recognized by the 26S proteasome, which degrades it into small peptides. This degradation process prevents the

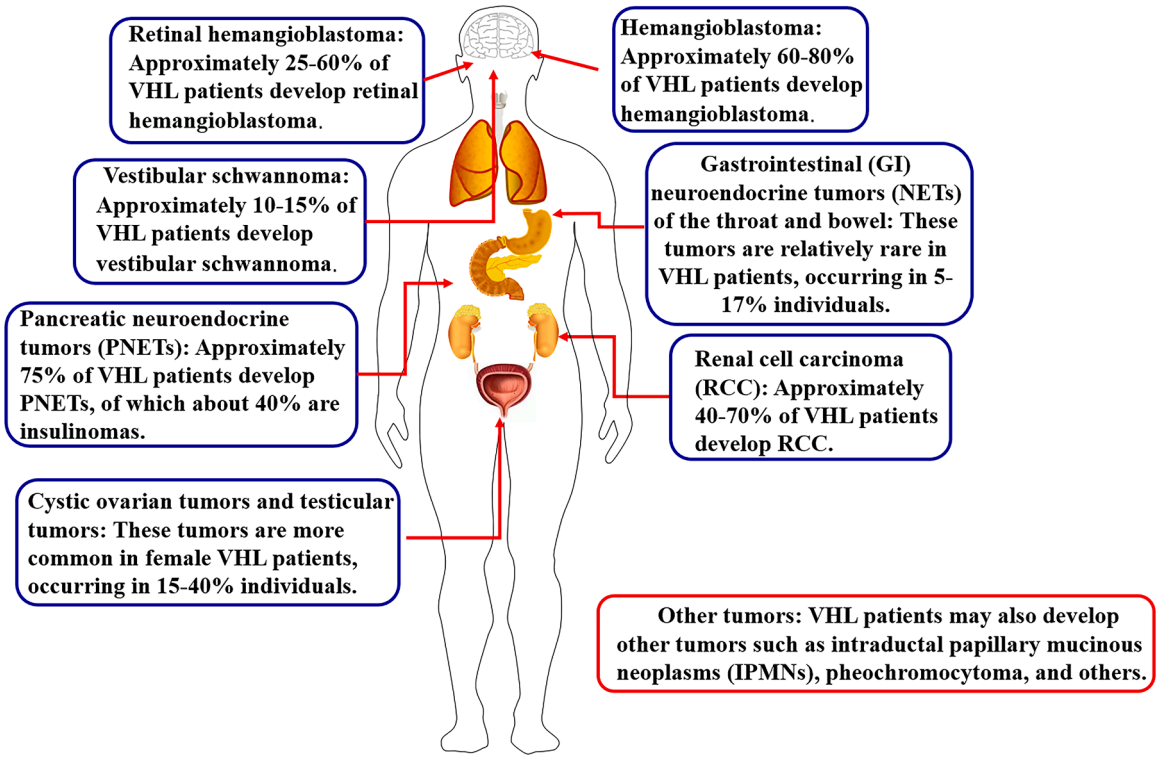

Fig. 1. Types and **percentages of tumors associated with VHL syndrome.**
VHL Syndrome is associated with the development of several types of tumors, including renal cell carcinoma (RCC), hemangioblastoma, and pheochromocytoma. Approximately 40-70% of individuals with VHL develop RCC, 60-80% develop hemangioblastomas (usually in the brain, spinal cord, or retina), and 10-20% develop pheochromocytomas (tumors that arise from cells in the adrenal glands). Other tumors associated with VHL syndrome include pancreatic cysts and neuroendocrine tumors, epididymal cystadenomas, and endolymphatic sac tumors. The percentage of individuals with VHL who develop these tumors varies widely.

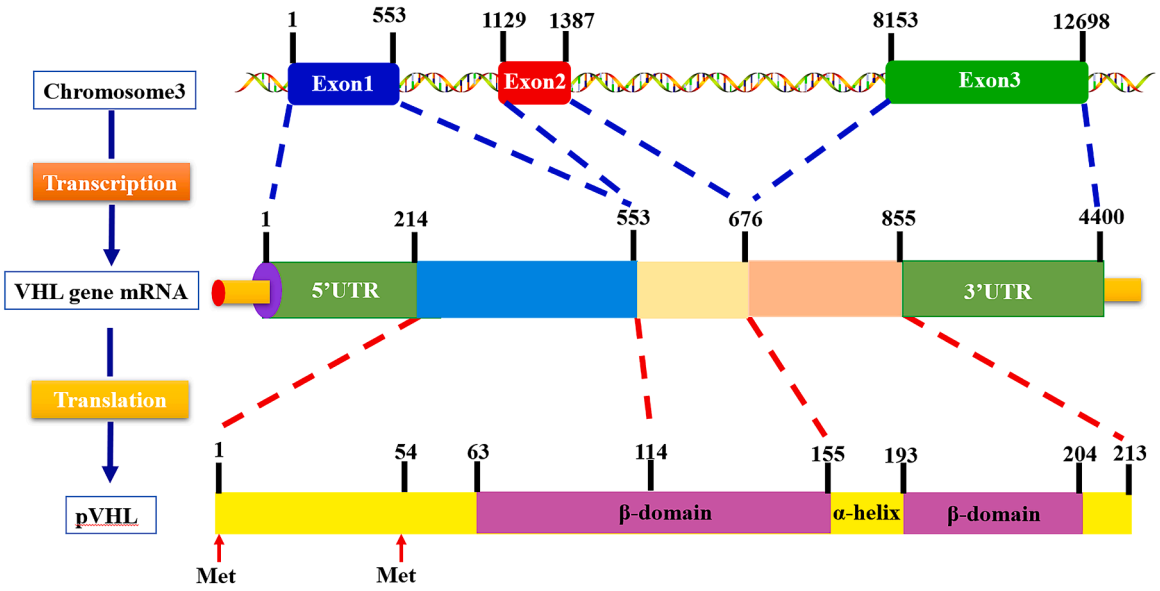

Fig. 2. The process of VHL gene transcription and translation.
The VHL gene is located on the short arm of chromosome 3 (3p25-26) and consists of three exons, with an open reading frame (ORF) of 854 nucleotides encoding 284 amino acid residues. The full length of the VHL gene is approximately 4.5 kb and it is distributed within a DNA space of approximately 20 kb. The complete coding sequence spans exon 1, exon 2 and part of exon 3 with an open reading frame (ORF) of 854 base pairs encoding a protein of 213 amino acids. The mRNA molecule undergoes alternative splicing at exon 2 and exon 3, resulting in two major isoforms: VHL30 and VHL19. The VHL protein contains two major domains: an N-terminal alpha domain composed of residues 1–53, which has a structural scaffold with distinct folding arrangements and allows for interaction with other proteins, and a C-terminal beta-domain composed of residues 54–213, which contains the highly conserved BC-box motif that mediates substrate binding and facilitates the recruitment of Elongin C and B-Cul2 to form the complex.

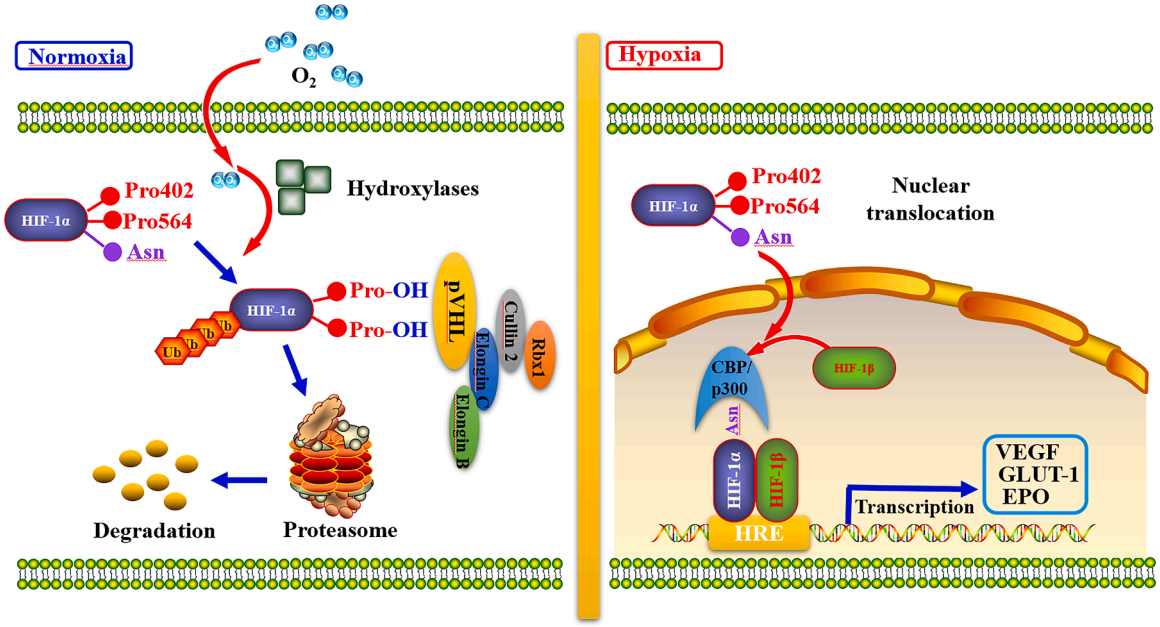

Fig. 3. The mechanism of HIF-1α expression regulated by pVHL.
pVHL is an E3 ubiquitin ligase that targets HIF-1α for degradation through the proteasome pathway under normal oxygen conditions. Under normoxic conditions, pVHL binds to specific hydroxylated proline residues in the oxygen-dependent degradation domain (ODDD) of HIF-1α, which leads to the addition of ubiquitin and subsequent degradation of HIF-1α by the proteasome. Under hypoxic conditions, the activity of PHDs is reduced due to a lack of oxygen. As a result, HIF-1α is no longer fully hydroxylated, which prevents pVHL from recognizing and targeting HIF-1α for degradation. Therefore, HIF-1α accumulates in the cell and translocates to the nucleus. In the nucleus, HIF-1α forms a heterodimer with HIF-1β and binds to hypoxia-response elements (HREs) located in the promoter regions of various genes, activating their expression.

accumulation of HIF-1α and thus limits the activation of HIF-1 target genes under normoxic conditions. Under hypoxic conditions, the proline residues in the ODD of HIF-1α are not hydroxylated, which prevents VHL from binding to HIF-1α. As a result, HIF-1α escapes VHL-mediated degradation and accumulates in the cell, leading to the activation of HIF-1 target genes. In addition to promoting HIF degradation, VHL can also inhibit HIF transcriptional activity by interacting with co-repressors such as HDAC1 and TLE1 [15].

Moreover, VHL can affect HIF mRNA stability and translation, leading to changes in HIF protein levels even in the absence of oxygen depletion [16,17]. In addition to VHL protein's role, HIF is also regulated by other factors such as acetylation, methylation modifications, etc., further fine-tuning the stability and activity of HIF in the cell. Studying the regulation relationship between HIF and VHL not only provides insights into the cell's response to hypoxia but also helps reveal the impact of hypoxic microenvironment on tumor growth and metastasis, offering new therapeutic targets and strategies for related diseases. Overall, the latest findings support the critical role of VHL in modulating HIF expression and function and highlight the complex interplay between these two molecules in regulating cellular responses to hypoxia [18].

2. Cyclin D1: VHL is a tumor suppressor gene that plays a crucial role in regulating the cell cycle and preventing uncontrolled cell growth. One of the key targets of VHL is Cyclin D1, a protein that promotes cell cycle progression by activating cyclin-dependent kinases (CDKs). Under normal conditions, VHL binds to and targets Cyclin D1 for degradation by the proteasome [19,20]. This prevents the accumulation of Cyclin D1 and keeps the cell cycle in check. However, in the absence of VHL, Cyclin D1 levels can become elevated, leading to uncontrolled cell growth and the development of tumors. Studies have shown that VHL regulates Cyclin D1 through multiple mechanisms. One of these involves HIF pathway, which is activated when cells are exposed to low oxygen levels [21]. Another mechanism involves the interaction between VHL and the E2F transcription factor, which plays a key role in regulating the expression of genes involved in cell cycle progression. VHL can bind to E2F and promote its degradation, which reduces the expression of Cyclin D1 [22]. Furthermore, it is fascinating to see how VHL serves as a crucial regulator in maintaining cell cycle homeostasis by targeting Cyclin D1 for degradation, ultimately preventing aberrant cell growth and tumor formation. These intricate molecular mechanisms highlight the importance of VHL in safeguarding cellular integrity and emphasize its potential significance in cancer therapeutics.
3. VEGF: Loss of VHL function leads to increased expression of VEGF, which can promote the growth and metastasis of tumors. In the absence of functional VHL, HIF is constitutively stabilized, resulting in persistent activation of VEGF signaling and the formation of highly vascularized tumors [23]. This mechanism is particularly important in certain types of cancer, such as renal cell carcinoma (RCC), where mutations in VHL are commonly found [24].

   In addition to its role in regulating HIF, VHL also interacts with other proteins involved in the regulation of VEGF expression. For example, VHL can bind to the RNA-binding protein HuR and promote its degradation, leading to a decrease in VEGF mRNA stability [25]. VHL can also interact with the E3 ubiquitin ligase Itch and promote the ubiquitination and degradation of VEGFR2, the receptor for VEGF [26]. In conclusion, in-depth research on the interaction between VHL and VEGF not only helps to understand the pathogenesis of tumors, but also provides important clues for the development of new tumor treatment methods. By regulating the activity of VHL and VEGF, more effective and targeted tumor treatments may be achieved in the future, which is of great significance for improving treatment outcomes and prognosis. Looking forward to further research bringing more breakthroughs and innovations to tumor treatment in the future.
4. GLUT1: Glucose transporter 1 (GLUT1) is a membrane protein that facilitates the uptake of glucose into cells and is upregulated in many types of cancer cells to support their high metabolic demands. It has been shown that VHL can bind to GLUT1 and promote its ubiquitination and degradation, thereby reducing glucose uptake and metabolism in cells. This occurs through a mechanism independent of HIF, as VHL can directly interact with GLUT1 and target it for degradation in a HIF-independent manner [27]. Loss of VHL function can lead to increased GLUT1 expression and enhanced glucose uptake, which can contribute to the growth and survival of cancer cells. This mechanism has been implicated in several types of cancer, including RCC and neuroendocrine tumors [28–30]. Recent studies have also revealed that VHL can regulate GLUT1 expression through other mechanisms, such as modulating the activity of the mTORC1 signaling pathway or interacting with other proteins such as TFE3 and PPARγ [31]. Therefore, targeting the VHL-GLUT1 axis could be a promising approach for cancer therapy.
5. c-Myc: VHL has been shown to negatively regulate c-MYC expression by promoting its proteasomal degradation. This occurs through a mechanism that involves VHL binding to the c-MYC protein and recruiting an E3 ubiquitin ligase complex to target it for degradation [32,33]. Loss of VHL function can lead to increased c-MYC expression and activation, which can contribute to the development and progression of cancer. The regulation of c-MYC by VHL is independent of HIF, indicating that VHL may have HIF-independent tumor suppressor functions. At the transcriptional level, VHL can inhibit c-MYC expression by recruiting histone deacetylases to its promoter region or by promoting the degradation of the RNA polymerase II subunit Rpb1 [34]. At the translational level, VHL can inhibit c-MYC translation by interacting with eukaryotic initiation factor 4E-binding protein 1 (4E-BP1), which sequesters the mRNA cap-binding protein eIF4E and prevents its assembly into the translation initiation complex [35]. Interestingly, recent studies have also suggested that c-MYC may in turn regulate VHL expression and function, creating a feedforward loop that could contribute to tumorigenesis [36,37]. Overall, these findings highlight the multifaceted nature of VHL regulation of c-MYC and suggest potential avenues for therapeutic intervention in cancers driven by dysregulated c-MYC expression

The regulation of pVHL function is complex and involves several signaling pathways, including the mTOR, Wnt, and Notch pathways. For example, mTOR activation can lead to the stabilization of HIF through the phosphorylation of pVHL, which impairs its ability to bind to HIF [38]. Similarly, activation of the Wnt and Notch pathways can also lead to the stabilization of HIF through the regulation of pVHL function. Mutations in the VHL gene lead to the loss of pVHL function, which results in the accumulation of HIF and the dysregulation of downstream signaling pathways [39,40]. The accumulation of HIF can lead to the development of tumors, as HIF promotes cell growth and survival under hypoxic conditions. It is fascinating how intricate the molecular mechanisms are in tumor development, and targeting specific pathways such as the interaction between VHL and VEGF could lead to significant advancements in cancer treatment. We believe that further research in this area will not only enhance our understanding of tumor biology but also pave the way for more personalized and effective therapies tailored to individual patients. This exciting potential for breakthroughs in cancer treatment motivates me to stay informed and hopeful for the future of oncology research.

Advancements in the treatment of von Hippel-Lindau (VHL) syndrome

Von Hippel-Lindau (VHL) disease affects multiple organs, including the brain, spinal cord, kidneys, pancreas, and adrenal glands. The loss of VHL function leads to the formation of benign or malignant tumors in these organs. Over the past few decades, significant progress has been made in the diagnosis and management of VHL syndrome. Early detection and surveillance of VHL-associated tumors are crucial for improving patient outcomes. Advances in imaging technologies, such as MRI and CT scans, have allowed for more accurate detection and monitoring of tumor growth. Currently, there is no cure for VHL disease, and treatment options are limited to surgery, radiation therapy, and drugs that target specific pathways involved in tumor growth (Fig. 4).

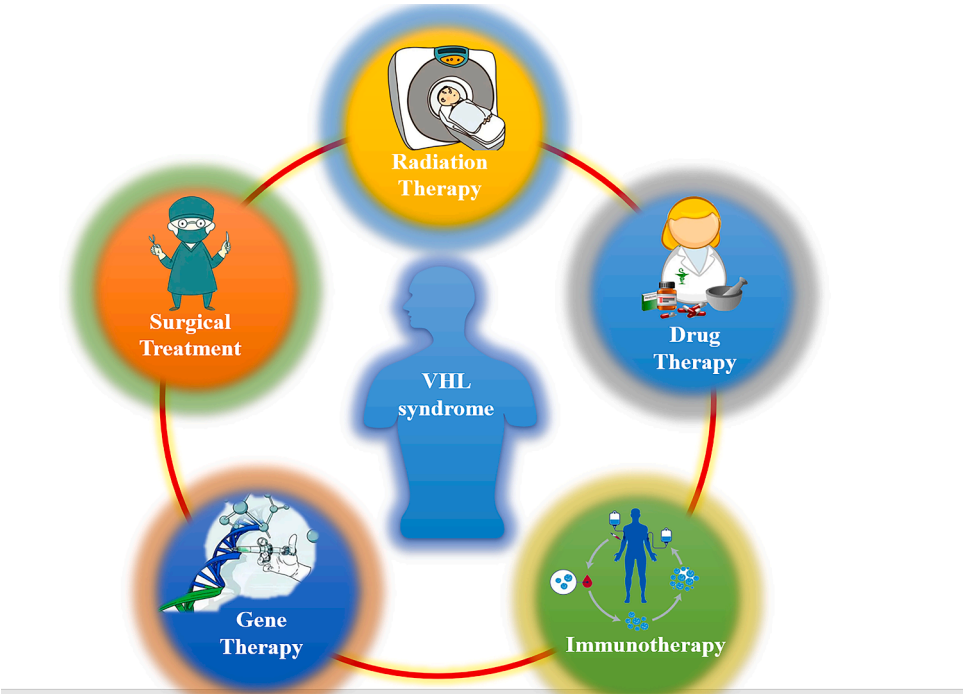

Fig. 4. The treatments of VHL syndrome.
VHL disease is a complicated disorder that requires a comprehensive treatment approach involving multiple disciplines. For localized tumors, surgery and radiation therapy are the primary treatments. However, for more advanced and metastatic tumors, drug therapy, gene therapy, and immunotherapy show promise as new treatment options. Further research is necessary to refine these approaches and enhance outcomes for individuals with VHL disease.

1. **Surgical Treatment:** Surgery is the primary treatment for VHL-related tumors that are localized and accessible. It involves removing the tumor or the affected organ, such as the kidney, adrenal gland, or pancreas. In recent years, kidney-sparing surgery has also gradually become an important treatment method, mainly including partial nephrectomy, kidney reconstruction after nephrectomy, renal artery embolization, etc [41]. In pancreatic neuroendocrine tumors, with the continuous improvement of surgical techniques, portal duodenectomy and pancreaticoduodenectomy have become the preferred methods for treating pancreatic neuroendocrine tumors [42]. While the development of endoscopic surgical techniques has made the treatment of pancreatic cystic tumors safer and more effective. VHL syndrome can also cause the occurrence of cerebral vascular tumors and olfactory neuroblastoma. In recent years, the development of minimally invasive surgical techniques has made brain surgery safer and more effective [43]. At the same time, selective arterial embolization and radiotherapy have also gradually been applied to the treatment of cerebral vascular tumors [44]. With the continuous improvement of surgical techniques, the safety and effectiveness of tumor resection are constantly improving. Overall, these advancements in surgical management offer hope for improved outcomes and quality of life for patients with VHL syndrome. However, continued research and innovation in this field will be necessary to further optimize surgical outcomes and reduce the burden of disease for affected individuals.
2. Radiation Therapy: Radiation therapy is used to treat VHL-related tumors that are not amenable to surgery, such as those in the brain and spinal cord. It uses high-energy radiation to destroy tumor cells or prevent their growth [45]. Recent advances in radiation therapy have shown promising results in the treatment of VHL-related pheochromocytomas, meningiomas and renal cell carcinomas. Newer techniques such as proton therapy and stereotactic radiotherapy have shown potential for effectively treating these tumors while minimizing damage to surrounding normal tissue [46]. In our view, it is essential to emphasize the importance of close monitoring to ensure the safety and efficacy of radiation therapy in VHL syndrome. Radiation therapy remains a crucial component in the treatment of VHL-related tumors and continues to evolve as a primary treatment option.
3. Drug Therapy: In addition to surgery and radiation therapy, drug therapy has become an important approach to treating VHL syndrome. In recent years, there have been significant advances in drug therapy for VHL-related tumors, with targeted therapy being the most representative. Targeted therapy drugs for renal cell carcinoma, such as bevacizumab [47], sunitinib [48], cabozantinib [49], everolimus [50], and pazopanib [51,52], have been widely used in clinical practice. They have shown promising results in clinical trials, but their effectiveness and safety are still being evaluated. Despite these promising findings, drug therapy for VHL syndrome remains challenging due to the heterogeneity and complexity of VHL-related tumors.

   In April 2021, belzutifan received accelerated approval from the U.S. Food and Drug Administration (FDA) for the treatment of adult patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC) who require systemic therapy but are not eligible for surgery [53]. In pretreated ccRCC, belzutifan achieved disease control rate of 80% under the recommended dose of 120 mg orally daily in phase I trial [54]. In phase 2 trials evaluating patients with VHL-associated RCC, belzutifan also showed favorable efficacy in terms of overall response rate and disease stabilization among patients with previously untreated or progressive tumors [55]. Additionally, the drug exhibited a favorable safety profile. Recently, in another phase 2 trial, belzutifan plus cabozantinib has promising antitumour activity in 52 patients with pretreated clear cell renal cell carcinoma [56]. The approval of belzutifan represents a significant advancement in the targeted therapy for VHL disease, providing a novel treatment option for patients who previously had limited choices. It offers potential benefits in terms of tumor control, improved quality of life, and prolonged survival. Looking ahead, with more research and development of targeted drugs like

belzutifan, we can expect to see more innovative treatment options emerging for VHL syndrome patients. This will help improve their quality of life and potentially extend their lifespan.

In recent years, the development of novel VHL-targeted drugs using PROTAC technology (Proteolysis Targeting Chimeras) has received widespread attention and quickly become a forefront research hot topic. PROTAC technology is an innovative drug design strategy aimed at promoting the degradation of disease-relevant proteins by using fusion proteins to achieve therapeutic effects. PROTAC technology involves designing a specific fusion protein, with one end binding to the disease-relevant protein (such as HIF-α) and the other end binding to ubiquitin ligase, allowing the fusion protein to mark the target protein for degradation [57,58]. Subsequently, the fusion protein delivers the target protein to the proteasome for degradation, effectively inhibiting the biological activity of the disease-relevant protein and thereby achieving therapeutic effects. In VHL syndrome, PROTAC technology can be applied to design targeted drugs against HIF-α protein, inhibiting its overexpression by promoting its degradation, and inhibiting tumor formation. Although research on the application of this technology in VHL syndrome treatment is still in its early stages, its success in treating other diseases provides a strong foundation for its application in VHL syndrome. In the future, with further research into the pathophysiology of VHL syndrome and PROTAC technology, it is believed that this technology will provide more precise and effective treatment options for VHL syndrome patients. Further experiments and clinical studies will help validate the feasibility and efficacy of PROTAC technology in the treatment of VHL syndrome, laying a solid foundation for its future clinical application.

4. Gene Therapy: Gene therapy is a promising approach to treating VHL disease. It involves replacing or repairing the mutated VHL gene in cells affected by the disease. Several strategies have been developed to deliver functional VHL genes to target cells, such as viral vectors [58,59], liposomes [60], and nanoparticles [61,62]. Recent research on VHL syndrome gene therapy has focused on the use of adenoviral vectors to deliver functional VHL genes to cells with VHL mutations [63]. Additionally, CRISPR/Cas9 gene editing technology has shown promise in correcting VHL mutations in cells [64,65]. These gene-based approaches have demonstrated efficacy in preclinical studies and are being tested for safety and efficacy in clinical trials. Another promising approach is the use of RNA interference (RNAi) to target VHL-related pathways [66,67]. RNAi is a natural cellular process that regulates gene expression, and RNAi-based therapies have shown efficacy in preclinical studies for VHL-related tumors. Despite these promising findings, gene therapy for VHL syndrome is still in the early stages of development and faces significant challenges. These challenges include the need for more efficient and specific delivery methods, concerns about the long-term safety and efficacy of gene therapy, and the high cost of treatment.
5. Immunotherapy: Immunotherapy is a novel approach to treating VHL-related tumors that harnesses the power of the immune system to recognize and destroy cancer cells [68,69]. Recent studies have also explored the use of immunotherapy in VHL-related tumors. One type of immunotherapy that has shown promise in treating VHL-related tumors is immune checkpoint inhibitors, such as nivolumab [70] and pembrolizumab [71]. These drugs target molecules on immune cells that regulate the immune response, allowing the immune system to attack cancer cells more effectively. Clinical trials of immune checkpoint inhibitors in VHL-related renal cell carcinoma (RCC) have shown promising results, with some patients achieving durable responses. Another promising approach is the use of vaccines to stimulate the immune system to recognize and attack VHL-related tumors. Vaccines can be designed to target specific antigens expressed by VHL-related tumors, potentially leading to more specific and effective immune responses. Clinical trials of vaccines in VHL-related RCC and hemangioblastomas are currently underway [72,73]. However, it is also important to consider that the efficacy of immunotherapy can vary depending on the specific subtype of VHL-related tumors and the individual response of patients to treatment. In addition, ongoing research is focused on developing novel immunotherapy approaches that can overcome the challenges posed by the immunosuppressive tumor microenvironment in VHL-related tumors. By combining immunotherapy with targeted therapies or other treatment modalities, there is potential to enhance the overall response rates and outcomes for patients with VHL-related tumors.

VHL disease is a complex and challenging disorder that requires a multidisciplinary approach to treatment. Surgery and radiation therapy remain the mainstays of treatment for localized tumors, while drug therapy, gene therapy, and immunotherapy offer new and promising options for advanced and metastatic tumors. Further research is needed to optimize these approaches and improve the outcomes for patients with VHL disease.

Advances in diagnostic and monitoring biomarkers for VHL syndrome

The diagnosis and monitoring of VHL syndrome can be challenging due to the wide range of clinical manifestations and the variable disease course. However, recent advances in the identification of biomarkers have shown promise in improving the diagnosis and monitoring of the disease.

1. Biomarkers for Hemangioblastomas: Hemangioblastomas are a common type of tumor associated with VHL syndrome. To aid in diagnosis and monitoring of these tumors, several studies have explored the use of circulating biomarkers. For instance, research has shown that plasma levels of vascular endothelial growth factor (VEGF) are significantly higher in individuals with hemangioblastomas compared to healthy controls [74,75]. Another study has found that levels of circulating endothelial cells (CECs) and endothelial progenitor cells (EPCs) were elevated in VHL patients with hemangioblastomas, suggesting that these cells hold potential as useful biomarkers for disease monitoring [76,77].
2. Biomarkers for Renal Cell Carcinoma: Renal cell carcinoma (RCC) is a prevalent tumor observed in individuals with VHL syndrome. While surgical removal is the conventional method of treating RCC, reliable biomarkers for early detection and disease monitoring are necessary. Studies exploring circulating biomarkers have found promising results. For example, research demonstrated that serum levels of matrix metalloproteinase-9 (MMP-9) were significantly higher in VHL patients with RCC than those without RCC [78]. Additionally, elevated plasma levels of von Willebrand factor (vWF) were identified in VHL patients with RCC, suggesting that vWF could serve as a valuable biomarker for RCC evaluation [79].
3. Pheochromocytoma is a rare tumor closely associated with VHL syndrome. The tumor originates from the chromaffin cells located in the adrenal medulla and results in excess production of catecholamines, causing hypertension and other related symptoms. Various studies have explored potential biomarkers for diagnosing and tracking pheochromocytoma in individuals with VHL syndrome. One such study found that plasma levels of chromogranin A (CgA) were significantly higher in VHL patients with pheochromocytoma than those without the condition [80]. Another investigation revealed elevated plasma levels of metanephrines and normetanephrines in VHL patients with pheochromocytoma, suggesting that these metabolites could serve as valuable biomarkers for disease monitoring [81]. Additionally, advancements in imaging techniques and genetic testing may play a key role in improving early detection and personalized treatment strategies for patients with VHL-related pheochromocytoma. These multidisciplinary approaches could

ultimately lead to better outcomes and quality of life for affected individuals.

4. Biomarkers for Pancreatic Neuroendocrine Tumors: Pancreatic neuroendocrine tumors (PNETs) are a rare tumor associated with VHL syndrome. The tumors arise from the islet cells of the pancreas and can produce excess hormones, leading to symptoms such as hypoglycemia and hyperinsulinemia. Biomarkers for the diagnosis and monitoring of PNETs in VHL patients are needed. One study found that serum levels of neuron-specific enolase (NSE) were significantly higher in VHL patients with PNETs compared to those without PNETs [82]. Another study showed that plasma levels of chromogranin A (CgA) were significantly higher in VHL patients with PNETs, suggesting that CgA may be a useful biomarker for disease monitoring [83]. While the identification of biomarkers like NSE and CgA shows promise in aiding the diagnosis and monitoring of PNETs in VHL patients, ongoing research is crucial to explore additional biomarkers that can provide a more comprehensive understanding of disease progression and treatment response. Moreover, advancements in imaging technologies and genetic testing hold potential for enhancing the early detection and personalized management of VHL-related PNETs. By integrating these multidisciplinary approaches, healthcare professionals can optimize patient care and improve outcomes for individuals with VHL-associated pancreatic neuroendocrine tumors.
5. HIF2 and other potential biomarkers: In patients with VHL-associated clear cell renal cell carcinoma (ccRCC), HIF2 expression has been linked to poor response to targeted therapies, such as tyrosine kinase inhibitors (TKIs) like sunitinib and pazopanib[84]. High HIF2 levels have been associated with resistance to these therapies, suggesting that HIF2 expression could serve as a predictive biomarker for treatment response. While HIF2 is often associated with treatment resistance, recent studies have shown that acquired mutations in the HIF2 gene itself can confer resistance to HIF2 inhibitors [85]. These mutations prevent the binding of inhibitors and sustain HIF2 signaling, leading to ongoing tumor growth. Therefore, monitoring HIF2 mutations could be crucial in identifying patients who might develop resistance to HIF2-targeted therapies. Higher HIF2 levels have been associated with worse survival outcomes, shorter progression-free survival, and increased risk of disease recurrence after surgery [86]. Therefore, the expression levels of HIF2 could be valuable in predicting the clinical trajectory of VHL-associated tumors and informing treatment choices. It is essential to recognize that although HIF2 shows promise as a biomarker, additional research is required to comprehensively grasp its predictive and prognostic significance in VHL disease.

Additional biomarkers, such as VEGF, PDGF, MicroRNAs, and genetic profiling, are also being explored to improve the management and treatment outcomes for VHL patients. High levels of VEGF have been associated with aggressive tumor behavior in VHL-related tumors [87]. Monitoring VEGF expression or circulating VEGF levels may serve as a biomarker for tumor progression and response to treatment. Elevated levels of PDGF have been found in VHL-associated tumors, and targeting PDGF signaling pathways has shown potential as a therapeutic approach [88]. Assessing PDGF expression and its correlation with treatment response could help predict patient outcomes. Altered expression of specific miRNAs has been reported in VHL-related tumors, suggesting their potential as biomarkers. For example, miR-210 has been found to be upregulated in VHL-associated renal cell carcinoma (RCC) and has been associated with poor prognosis [89]. Other biomarkers being explored in VHL disease include markers of DNA methylation, chromosomal abnormalities, and immune response. These biomarkers may contribute to the understanding of disease prognosis, treatment response, and the development of personalized therapies.

In addition to these studies, researchers have also investigated the use of imaging biomarkers for the diagnosis and monitoring of VHL syndrome. For example, magnetic resonance imaging (MRI) and computed tomography (CT) scans are commonly used to detect and monitor the growth of kidney tumors in patients with VHL syndrome. Other imaging biomarkers, such as diffusion-weighted MRI, have shown promise in detecting and monitoring the growth of pancreatic tumors in patients with VHL syndrome. CTCs, miRNAs, and metabolites are promising biomarkers that have shown potential in recent studies [90]. Overall, the identification of biomarkers for VHL syndrome has the potential to improve the diagnosis and monitoring of the disease, as well as aid in the development of targeted treatments. In future research, in addition to discovering and validating biomarkers for VHL syndrome, attention should also be focused on how to effectively translate these biomarkers into diagnostic tools and treatment guidance in clinical practice. Furthermore, researchers should prioritize exploring new treatment strategies and drug targets to achieve more effective management of VHL syndrome. By integrating biomarkers and novel treatment approaches, we can potentially offer patients more comprehensive and personalized medical care to better cope with the challenges posed by VHL syndrome.

Optimizing disease management of VHL syndrome patients

The management of VHL disease requires a multidisciplinary approach that involves close collaboration between healthcare providers, patients, and their families [91–93]. Therefore, optimizing the management of VHL patients requires a comprehensive consideration of treatment strategies, follow-up, and monitoring for different types of tumors.

1. Treatment Strategies: The treatment of VHL-related tumors depends on the location, size, and aggressiveness of the tumor, as well as the patient's overall health and preferences. Surgery is the primary treatment for localized tumors that are accessible, while radiation therapy is used for tumors that are not amenable to surgery. Drug therapy, gene therapy, and immunotherapy are emerging approaches that offer new options for advanced and metastatic tumors, but their effectiveness and safety are still being evaluated. The treatment of VHL-related tumors should be individualized and based on a comprehensive evaluation of the patient's condition [94].
2. Follow-up and Monitoring: VHL disease is a lifelong condition that requires regular follow-up and monitoring to detect and manage new or recurrent tumors. The frequency and type of follow-up depend on the patient's age, tumor burden, and risk of developing new tumors. For example, patients with VHL-related renal cell carcinoma should undergo regular imaging studies, such as MRI or CT scans, to detect new or growing tumors. Patients with VHL-related pheochromocytoma should undergo regular blood and urine tests to monitor hormone levels and blood pressure. Patients with VHL-related pancreatic tumors should undergo regular imaging studies and endoscopic ultrasound to detect new or growing tumors [95].
3. Psychological Support: VHL disease not only affects the physical health of patients but also takes a toll on their emotional and psychological well-being. In addition to providing psychological support through counseling, education, and support groups, it is important to address the social and financial burdens that come with managing a chronic illness. By offering comprehensive care that includes support for the patient's emotional, social, and financial needs, healthcare providers can help improve the patient's overall quality of life and well-being. It is essential to take a holistic approach to care for VHL patients, addressing not just their medical needs but also their psychological and social challenges

In summary, the treatment of VHL-related tumors should be individualized and based on a comprehensive evaluation of the patient's

condition. Regular follow-up and monitoring are essential to detect and manage new or recurrent tumors. In addition to individualized treatment and regular follow-up, it is important to consider the impact of VHL disease on the patient's daily life and relationships. Offering support services such as occupational therapy, social work assistance, and genetic counseling can help patients navigate the challenges of living with a chronic illness. Furthermore, involving the patient's family and caregivers in the treatment plan can strengthen the support network and improve the patient's overall well-being. By addressing the physical, emotional, social, and practical aspects of VHL disease, healthcare providers can provide comprehensive care that enhances the patient's quality of life.

The future outlook for VHL disease research

In recent years, significant progress has been made in understanding the molecular mechanisms underlying VHL disease, leading to the development of targeted therapies for VHL-associated tumors. In the future research, molecular mechanism research in predicting the progression of VHL disease can further explore the genetic variations and epigenetic regulation in tumor cells, as well as the cell signaling and metabolic regulation in the tumor microenvironment, to deeply analyze aspects such as tumor growth, spread, and drug resistance. For example, by studying the regulatory role of the VHL gene in key pathways such as angiogenesis and lactate metabolism, its mechanism in the process of tumor progression can be revealed, providing more accurate predictions for tumor growth, recurrence, and metastasis. In terms of prevention, molecular mechanism research can help deepen the understanding of the function and regulatory network of the VHL gene, including the regulation of processes such as autophagy, angiogenesis, cell adhesion, and apoptosis, to discover potential preventative strategies and interventions. By targeting VHL gene mutations and related pathways, the onset and progression of VHL-related tumors can be prevented or delayed, providing more effective preventive measures for high-risk individuals. In personalized treatment, molecular mechanism research can help identify the differences in response to specific treatment methods among different patients, including chemotherapy, targeted therapy, and immunotherapy. Through molecular subtyping and biomarker screening, the most suitable treatment plan can be tailored for each patient, improving the specificity and effectiveness of treatment.

Future trends in research methods and technologies include the use of single-cell multi-omics technologies to study tumor heterogeneity and evolution, utilizing artificial intelligence and machine learning algorithms to explore potential correlations and patterns in big data for more accurate prediction models and personalized medical solutions. Additionally, the application of tissue engineering and organ-on-a-chip technologies can simulate the complex interactions in the tumor microenvironment, providing more realistic and reliable models and platforms for disease prediction and treatment. Through continuous innovation and interdisciplinary collaboration, molecular mechanism research will play an increasingly important role in predicting, preventing, and treating VHL disease.

Looking forward, the direction of VHL disease research is likely to focus on the following areas:

1. Understanding the Pathogenesis: One of the key challenges in VHL disease research is to better understand the pathogenesis of the disease. VHL disease is caused by mutations in the VHL gene, which normally suppresses the growth of tumors. However, the precise mechanisms by which VHL gene mutations lead to tumor formation and progression are not fully understood. Future research should focus on elucidating the molecular and cellular pathways that are involved in VHL-related tumorigenesis, such as hypoxia signaling, angiogenesis, and metabolism.
2. Developing Effective Treatments: Another important area of research is the development of more effective treatments for VHL-related tumors. While surgery and radiation therapy are effective in controlling localized tumors, they have limited effectiveness against advanced and metastatic tumors. Drug therapy, gene therapy, and immunotherapy are emerging approaches that offer new options for advanced and metastatic tumors, but their effectiveness and safety are still being evaluated. Future research should focus on identifying new targets and pathways for drug development, optimizing gene therapy and immunotherapy approaches, and developing better biomarkers for patient selection and monitoring.
3. Identifying Biomarkers: Biomarkers are important tools for the diagnosis, prognosis, and treatment of VHL disease. Currently, there are limited biomarkers available for VHL-related tumors, and their accuracy and specificity are often limited. Future research should focus on identifying and validating new biomarkers, such as circulating tumor cells, microRNAs, and metabolites, that can provide more accurate and specific information about VHL-related tumors.
4. Applying Technological Advances:In the future, VHL syndrome is poised to benefit from technological advances like Next-Generation Sequencing (NGS). NGS enables more accurate and early diagnosis, leading to personalized treatments and targeted therapies. This comprehensive genetic analysis can lead to a deeper understanding of VHL syndrome's genetic basis, including the identification of rare variants and novel disease-associated genes. This increased knowledge will refine diagnostic approaches and enable personalized treatment strategies. Emerging technologies like CRISPR-Cas9 gene editing hold promise for the treatment of genetic disorders like VHL syndrome. While still in the early stages of development, gene editing approaches may offer the potential to correct VHL gene mutations directly or modify the expression of genes involved in disease progression. Immune-based therapies and the integration of NGS data with artificial intelligence can optimize treatment strategies. Collaboration and knowledge sharing among researchers are also expected to accelerate advancements in VHL syndrome.

In summary, this review consolidates the latest advancements in VHL disease research, providing a comprehensive understanding of its molecular mechanisms, clinical presentations, management strategies, and psychosocial considerations. By delving into recent discoveries and ongoing research, this review adds to the existing literature and knowledge on VHL disease by synthesizing the most up-to-date information. This comprehensive overview serves as a valuable resource for healthcare professionals, researchers, and patients, ultimately aiding in improved diagnosis, treatment, and patient care for individuals affected by VHL disease.

VHL disease is a complex and challenging disorder that requires a multidisciplinary approach to research and development. The future of VHL disease research and development lies in understanding its underlying mechanisms, developing more effective treatments, and identifying better biomarkers for diagnosis and monitoring. With continued research and collaboration, we can improve the outcomes for patients with VHL disease and ultimately find a cure for this rare genetic disorder.

CRediT authorship contribution statement

Yaochun Wang: Writing – original draft, Writing – review & editing. **Jingzhuo Song:** Writing – original draft, Writing – review & editing. **Shuxing Zheng:** Formal analysis, Investigation, Resources. **Shuhong Wang:** Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

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References

[1] M Louise, M Binderup, M Smerdel, L Borgwadt, SS Beck Nielsen, MG Madsen, HU Møller, JF Kiilgaard, L Friis-Hansen, V Harbud, S Cortnum, H Owen, S Gimsing, HA Friis Juhl, S Munthe, M Geilswijk, ÅK Rasmussen, U Møldrup, O Graumann, F Donskov, H Grønbæk, B Stausbøl-Grøn, O Schaffalitzky de Muckadell, U Knigge, G Dam, KA Wadt, L Bøgeskov, P Bagi, L Lund, K Stochholm, LB Ousager, Sunde L. von, Hippel-Lindau disease: Updated guideline for diagnosis and surveillance, Eur. J. Med. Genet. 65 (8) (2022) 104538.
[2] WG Kaelin Jr., Von Hippel-Lindau disease: insights into oxygen sensing, protein degradation, and cancer, J. Clin. Invest. 132 (18) (2022) e162480.
[3] A Larcher, I Rowe, F Belladelli, G Fallara, D Raggi, A Necchi, F Montorsi, U Capitanio, A Salonia, OSR VHL Program. Von Hippel-Lindau disease-associated renal cell carcinoma: a call to action, Curr. Opin. Urol. 32 (1) (2022) 31–39.
[4] NH Shirole, WG Kaelin Jr., von-Hippel Lindau and hypoxia-inducible factor at the center of renal cell carcinoma biology, Hematol. Oncol. Clin. North Am. 37 (5) (2023) 809–825.
[5] N Ayub, AJAT Braat, HJLM Timmers, MGEH Lam, RS. van Leeuwaarde, Challenges in Von Hippel-Lindau's disease: PRRT in patients on hemodialysis, Endocrinol. Diabetes. Metab. Case Rep. 2022 (2022) 21–0195.
[6] K Tamura, Y Kanazashi, C Kawada, Y Sekine, K Maejima, S Ashida, T Karashima, S Kojima, NF Parrish, S Kosugi, C Terao, S Sasagawa, M Fujita, TA Johnson, Y Momozawa, K Inoue, T Shuin, H. Nakagawa, Variant spectrum of von Hippel-Lindau disease and its genomic heterogeneity in Japan, Hum. Mol. Genet. 32 (12) (2023) 2046–2054.
[7] JR Gnarra, K Tory, Y Weng, L Schmidt, MH Wei, H Li, F Latif, S Liu, F Chen, FM Duh, et al., Mutations of the VHL tumour suppressor gene in renal carcinoma, Nat. Genet. 7 (1) (1994) 85–90.
[8] C Blankenship, JG Naglich, JM Whaley, B Seizinger, N. Kley, Alternate choice of initiation codon produces a biologically active product of the von Hippel Lindau gene with tumor suppressor activity, Oncogene 18 (8) (1999) 1529–1535.
[9] J Hu, DJ Smith, L. Wu, VHL L169P variant does not alter cellular hypoxia tension in clear cell renal cell carcinoma, Int. J. Mol. Sci. 24 (18) (2023) 14075.
[10] G Minervini, F Quaglia, F Tabaro, SCE. Tosatto, Insights into the molecular features of the von Hippel-Lindau-like protein, Amino Acids 51 (10-12) (2019) 1461–1474.
[11] H Kanno, S Matsumoto, T Yoshizumi, K Nakahara, A Kubo, H Murata, T Shuin, U HS, Role of SOCS and VHL proteins in neuronal differentiation and development, Int. J. Mol. Sci. 24 (4) (2023) 3880.
[12] S Li, W Li, J Yuan, P Bullova, J Wu, X Zhang, Y Liu, M Plescher, J Rodriguez, OC Bedoya-Reina, PR Jannig, P Valente-Silva, M Yu, MA Henriksson, RA Zubarev, A Smed-Sörensen, CK Suzuki, JL Ruas, J Holmberg, C Larsson, C Christofer Juhlin, A von Kriegsheim, Y Cao, S Schlisio, Impaired oxygen-sensitive regulation of mitochondrial biogenesis within the von Hippel-Lindau syndrome, Nat. Metab. 4 (6) (2022) 739–758.
[13] P Hudler, M. Urbancic, The role of VHL in the development of von Hippel-Lindau disease and erythrocytosis, Genes 13 (2) (2022) 362.
[14] LP Vu, CJ Diehl, R Casement, AG Bond, C Steinebach, N Strašek, A Bricelj, A Perdih, G Schnakenburg, I Sosič, A Ciulli, M. Gütschow, Expanding the structural diversity at the phenylene core of ligands for the von Hippel-Lindau E3 ubiquitin ligase: development of highly potent hypoxia-inducible factor-1α stabilizers, J. Med. Chem. 66 (18) (2023) 12776–12811.
[15] Y Zhao, W Xiong, C Li, R Zhao, H Lu, S Song, Y Zhou, Y Hu, B Shi, J. Ge, Hypoxia-induced signaling in the cardiovascular system: pathogenesis and therapeutic targets, Signal. Transduct. Target. Ther. 8 (1) (2023) 431.
[16] X Liu, H Deng, J Tang, Z Wang, C Zhu, X Cai, F Rong, X Chen, X Sun, S Jia, G Ouyang, W Li, W Xiao, OTUB1 augments hypoxia signaling via its non-canonical ubiquitination inhibition of HIF-1α during hypoxia adaptation, Cell Death. Dis. 13 (6) (2022) 560.
[17] S Peng, J Zhang, X Tan, Y Huang, J Xu, N Silk, D Zhang, Q Liu, J. Jiang, The VHL/HIF axis in the development and treatment of pheochromocytoma/paraganglioma, Front. Endocrinol. 11 (2020) 586857.
[18] CB Nguyen, E Oh, P Bahar, UN Vaishampayan, T Else, AS Alva, Novel approaches with HIF-2α targeted therapies in metastatic renal cell carcinoma, Cancers 16 (3) (2024) 601.
[19] S Mazumder, PJ Higgins, R. Samarakoon, Downstream targets of VHL/HIF-α signaling in renal clear cell carcinoma progression: mechanisms and therapeutic relevance, Cancers 15 (4) (2023) 1316.
[20] WG Kaelin Jr., The von Hippel-Lindau gene, kidney cancer, and oxygen sensing, J. Am. Soc. Nephrol. 14 (11) (2003) 2703–2711.
[21] SC Li, LJ Yan, XL Wei, ZK Jia, JJ Yang, XH. Ning, A novel risk model of three SUMOylation genes based on RNA expression for potential prognosis and treatment sensitivity prediction in kidney cancer, Front. Pharmacol. 14 (2023) 1038457.
[22] J Fallah, BI. Rini, HIF inhibitors: status of current clinical development, Curr. Oncol. Rep. 21 (1) (2019) 6.
[23] TK Choueiri, WG Kaelin Jr., Targeting the HIF2-VEGF axis in renal cell carcinoma, Nat. Med. 26 (10) (2020) 1519–1530.
[24] S Danilin, C Sourbier, L Thomas, S Rothhut, V Lindner, JJ Helwig, D Jacqmin, H Lang, T. Massfelder, von Hippel-Lindau tumor suppressor gene-dependent mRNA stabilization of the survival factor parathyroid hormone-related protein in human renal cell carcinoma by the RNA-binding protein HuR, Carcinogenesis 30 (3) (2009) 387–396.
[25] D Aki, Q Li, H Li, YC Liu, JH. Lee, Immune regulation by protein ubiquitination: roles of the E3 ligases VHL and Itch, Protein Cell 10 (6) (2019) 395–404.
[26] R Janostiak, A Torres-Sanchez, F Posas, E. de Nadal, Understanding retinoblastoma post-translational regulation for the design of targeted cancer therapies, Cancers 14 (5) (2022) 1265.
[27] W Zhang, X Zhou, Q Yao, Y Liu, H Zhang, Z. Dong, HIF-1-mediated production of exosomes during hypoxia is protective in renal tubular cells, Am. J. Physiol. Renal. Physiol. 313 (4) (2017) F906–F913.
[28] M Matsumoto, D Rokunohe, T Sasaki, Y Matsuzaki, H Nakano, H Mizukami, E Akasaka, D. Sawamura, Upregulated expression of glucose transporter isoform 1 in invasive and metastatic extramammary Paget's disease, Exp. Ther. Med. 27 (5) (2024) 228.
[29] ES Ildiz, A Gvozdenovic, WJ Kovacs, N. Aceto, Travelling under pressure - hypoxia and shear stress in the metastatic journey, Clin. Exp. Metastasis 40 (5) (2023) 375–394.
[30] YH Gao, ZX Wu, LQ Xie, CX Li, YQ Mao, YT Duan, B Han, SF Han, Y Yu, HJ Lu, PY Yang, TR Xu, JL Xia, GQ Chen, LS. Wang, VHL deficiency augments anthracycline sensitivity of clear cell renal cell carcinomas by down-regulating ALDH2, Nat. Commun. 8 (2017) 15337.
[31] D Zhou, Y Yao, L Zong, G Zhou, M Feng, J Chen, G Liu, G Chen, K Sun, H Yao, Y Liu, X Shi, W Zhang, B Shi, Q Tai, G Wu, L Sun, W Hu, X Zhu, S. He, TBK1 Facilitates GLUT1-dependent glucose consumption by suppressing mtorc1 signaling in colorectal cancer progression, Int. J. Biol. Sci. 18 (8) (2022) 3374–3389.
[32] SA Patel, S Hirosue, P Rodrigues, E Vojtasova, EK Richardson, J Ge, SE Syafruddin, A Speed, EK Papachristou, D Baker, D Clarke, S Purvis, L Wesolowski, A Dyas, L Castillon, V Caraffini, D Bihary, C Yong, DJ Harrison, GD Stewart, MJ Machiela, MP Purdue, SJ Chanock, AY Warren, SA Samarajiwa, JS Carroll, S. Vanharanta, The renal lineage factor PAX8 controls oncogenic signalling in kidney cancer, Nature 606 (7916) (2022) 999–1006.
[33] X Yu, D Li, J Kottur, Y Shen, HS Kim, KS Park, YH Tsai, W Gong, J Wang, K Suzuki, J Parker, L Herring, Kaniskan HÜ, L Cai, R Jain, J Liu, AK Aggarwal, GG Wang, J Jin, A selective WDR5 degrader inhibits acute myeloid leukemia in patient-derived mouse models, Sci. Transl. Med. 13 (613) (2021) eabj1578.
[34] S Strocchi, F Reggiani, G Gobbi, A Ciarrocchi, V. Sancisi, The multifaceted role of EGLN family prolyl hydroxylases in cancer: going beyond HIF regulation, Oncogene 41 (29) (2022) 3665–3679.
[35] Q Li, X Feng, F Niu, J Yang, Y Xu, X Pu, J Chen, X Fan, B Jiang, Q. Huang, Inhibition of p22phox suppresses epithelial ovarian cancer cell proliferation and tumorigenesis, J. Cancer 12 (14) (2021) 4277–4287.
[36] Y Zhou, X Gao, M Yuan, B Yang, Q He, J. Cao, Targeting Myc interacting proteins as a winding path in cancer therapy, Front. Pharmacol. 12 (2021) 748852.
[37] Z Chen, F Han, Y Du, H Shi, W. Zhou, Hypoxic microenvironment in cancer: molecular mechanisms and therapeutic interventions, Signal. Transduct. Target. Ther. 8 (1) (2023) 70.
[38] A Ganner, C Gehrke, M Klein, L Thegtmeier, T Matulenski, L Wingendorf, L Wang, F Pilz, L Greidl, L Meid, F Kotsis, G Walz, IJ Frew, Neumann-Haefelin E. VHL suppresses RAPTOR and inhibits mTORC1 signaling in clear cell renal cell carcinoma, Sci. Rep. 11 (1) (2021) 14827.
[39] J Ji, Y Xu, M Xie, X He, D Ren, T Qiu, W Liu, Z Chen, W Shi, Z Zhang, X Wang, W Wang, J Ma, Q Qian, A Jing, X Ma, J Qin, Y Ding, T Geng, J Yang, Z Sun, W Liu, S Liu, B Liu, VHL-HIF-2α axis-induced SEMA6A upregulation stabilized β-catenin to drive clear cell renal cell carcinoma progression, Cell Death. Dis. 14 (2) (2023) 83.
[40] A Arreola, LB Payne, MH Julian, AA de Cubas, AB Daniels, S Taylor, H Zhao, J Darden, VL Bautch, WK Rathmell, JC Chappell, Von Hippel-Lindau mutations disrupt vascular patterning and maturation via Notch, JCI Insight 3 (4) (2018) e92193.
[41] A Ghoreifi, R Sari Motlagh, G Fuchs, Modern Kidney-Sparing management of upper tract urothelial carcinoma, Cancers 15 (18) (2023) 4495.
[42] F Uccelli, F Gavazzi, G Capretti, M Virdis, M Montorsi, A. Zerbi, Parenchyma-sparing surgery for pancreatic endocrine tumors, Updates. Surg. 68 (3) (2016) 313–319.
[43] MT Krüger, C Steiert, S Gläsker, JH. Klingler, Minimally invasive resection of spinal hemangioblastoma: feasibility and clinical results in a series of 18 patients, J. Neurosurg. Spine (2019) 1–10.
[44] Y Bian, Y Xu, Y Xu, Z Li, W Zhu, X Zhou, Y Liu, B Feng, B Chen, X. Weng, Surgical treatment for pelvic haemophilic pseudotumour: a retrospective analysis of 21 cases, EClinicalMedicine 69 (2024) 102497.
[45] MC Bosco, G D'Orazi, D Del Bufalo, Targeting hypoxia in tumor: a new promising therapeutic strategy, J. Exp. Clin. Cancer Res. 39 (1) (2020) 8.
[46] K Kawaguchi, K Yashima, Y Ikebuchi, A Yoshida, S Kuwamoto, H. Isomoto, The first case of gastric neuroendocrine tumors induced by a proton pump inhibitor in von Hippel-Lindau disease, Intern. Med. 61 (17) (2022) 2587–2592.

[47] RJ Motzer, R Banchereau, H Hamidi, T Powles, D McDermott, MB Atkins, B Escudier, LF Liu, N Leng, AR Abbas, J Fan, H Koeppen, J Lin, S Carroll, K Hashimoto, S Mariathasan, M Green, D Tayama, PS Hegde, C Schiff, MA Huseni, B. Rini, Molecular subsets in renal cancer determine outcome to checkpoint and angiogenesis blockade, Cancer Cell 38 (6) (2020) 803–817.e4.
[48] X Li, L Gao, L Zhang, H Sun, H. Gou, Third-line sunitinib treatment in a VHL-mutated metastatic intrahepatic cholangiocarcinoma: a case report and literature review, Cancer Biol. Ther. 21 (9) (2020) 785–789.
[49] A Desai, EJ. Small, Treatment of advanced renal cell carcinoma patients with cabozantinib, an oral multityrosine kinase inhibitor of MET, AXL and VEGF receptors, Future Oncol. 15 (20) (2019) 2337–2348.
[50] AA Lalani, DYC Heng, NS Basappa, L Wood, N Iqbal, D McLeod, D Soulières, C. Kollmannsberger, Evolving landscape of first-line combination therapy in advanced renal cancer: a systematic review, Ther. Adv. Med. Oncol. 14 (2022) 17588359221108685.
[51] SA Matloob, D Paraskevopoulos, SM O'Toole, W Drake, N Plowman, N Foroglou, VHL: trends and insight into a multi-modality, interdisciplinary approach for management of central nervous system hemangioblastoma, Acta Neurochir. Suppl. 135 (2023) 81–88.
[52] B Yang, Z Li, Y Wang, C Zhang, Z Zhang, X. Zhang, Central nervous system hemangioblastoma in a pediatric patient associated with von hippel-lindau disease: a case report and literature Review, Front. Oncol. 11 (2021) 683021.
[53] E Jonasch, F Donskov, O Iliopoulos, WK Rathmell, VK Narayan, BL Maughan, S Oudard, T Else, JK Maranchie, SJ Welsh, S Thamake, EK Park, RF Perini, WM Linehan, R Srinivasan, MK-6482-004 Investigators, Belzutifan for renal cell carcinoma in von Hippel-Lindau disease, N. Engl. J. Med. 385 (22) (2021) 2036–2046.
[54] WW Choi, JL Boland, A Kalola, J. Lin, Belzutifan (MK-6482): biology and clinical development in solid tumors, Curr. Oncol. Rep. 25 (2) (2023) 123–129.
[55] V Visweswaran, K. Pavithran, Belzutifan: a narrative drug review, Curr. Drug Res. Rev. 14 (2) (2022) 88–95.
[56] TK Choueiri, DF McDermott, J Merchan, TM Bauer, R Figlin, EI Heath, MD Michaelson, E Arrowsmith, A D'Souza, S Zhao, A Roy, R Perini, D Vickery, SS Tykodi, Belzutifan plus cabozantinib for patients with advanced clear cell renal cell carcinoma previously treated with immunotherapy: an open-label, single-arm, phase 2 study, Lancet Oncol. 24 (5) (2023) 553–562.
[57] C Wang, Y Zhang, J Wang, D. Xing, VHL-based PROTACs as potential therapeutic agents: recent progress and perspectives, Eur. J. Med. Chem. 227 (2022) 113906.
[58] N Setia, HTA Almuqdadi, M. Abid, Journey of Von Hippel-Lindau (VHL) E3 ligase in PROTACs design: From VHL ligands to VHL-based degraders, Eur. J. Med. Chem. 265 (2024) 116041.
[59] J Krieger, FJ Sorrell, AA Wegener, B Leuthner, F Machrouhi-Porcher, M Hecht, EM Leibrock, JE Müller, J Eisert, IV Hartung, S. Schlesiger, Systematic potency and property Assessment of VHL ligands and implications on PROTAC design, ChemMedChem. 18 (8) (2023) e202200615.
[60] C Li, S Hu, Y. Yue, Ultrasound microbubble-mediated VHL regulates the biological behavior of ovarian cancer cells, Ultrasound. Med. Biol. 47 (3) (2021) 723–732.
[61] N Trac, HS Oh, LI Jones, R Caliliw, S Ohtake, B Shuch, EJ. Chung, CD70-targeted micelles enhance HIF2α siRNA delivery and inhibit oncogenic functions in patient-derived clear cell renal carcinoma cells, Molecules 27 (23) (2022) 8457.
[62] Z Xu, G Shen, X Xia, X Zhao, P Zhang, H Wu, Q Guo, Z Qian, Y Wei, S. Liang, Comparisons of three polyethyleneimine-derived nanoparticles as a gene therapy delivery system for renal cell carcinoma, J. Transl. Med. 9 (2011) 46.
[63] C Chen, A Tian, M Zhao, X. Ma, Adenoviral delivery of VHL suppresses bone sarcoma cell growth through inhibition of Wnt/β-catenin signaling, Cancer Gene Ther. 26 (3-4) (2019) 83–93.
[64] N Sun, S Petiwala, C Lu, JE Hutti, M Hu, M Hu, MH Domanus, D Mitra, SN Addo, CP Miller, N. Chung, VHL synthetic lethality signatures uncovered by genotype-specific CRISPR-Cas9 screens, CRISPR J. 2 (2019) 230–245.
[65] S Schokrpur, J Hu, DL Moughon, P Liu, LC Lin, K Hermann, S Mangul, W Guan, M Pellegrini, H Xu, L. Wu, CRISPR-mediated VHL knockout generates an improved model for metastatic renal cell carcinoma, Sci. Rep. 6 (2016) 29032.
[66] S Gao, L Liu, Z Li, Y Pang, J Shi, F. Zhu, Seven novel genes related to cell proliferation and migration of VHL-mutated pheochromocytoma, Front. Endocrinol. 12 (2021) 598656.
[67] YH Gao, ZX Wu, LQ Xie, CX Li, YQ Mao, YT Duan, B Han, SF Han, Y Yu, HJ Lu, PY Yang, TR Xu, JL Xia, GQ Chen, LS. Wang, VHL deficiency augments anthracycline sensitivity of clear cell renal cell carcinomas by down-regulating ALDH2, Nat. Commun. 8 (2017) 15337.
[68] YW Chen, L Wang, J Panian, S Dhanji, I Derweesh, B Rose, A Bagrodia, RR. McKay, Treatment landscape of renal cell carcinoma, Curr. Treat. Options. Oncol. 24 (12) (2023) 1889–1916.
[69] C Ding, Z Song, A Shen, T Chen, A. Zhang, Small molecules targeting the innate immune cGAS–STING–TBK1 signaling pathway, Acta Pharm. Sin. B 10 (12) (2020) 2272–2298.
[70] T Goodstein, Y Yang, K Runcie, R Srinivasan, EA. Singer, Two is company, is three a crowd? Triplet therapy, novel molecular targets, and updates on the management of advanced renal cell carcinoma, Curr. Opin. Oncol. 35 (3) (2023) 206–217.
[71] PJ. Vlachostergios, Resistance to pembrolizumab and axitinib in renal cell carcinoma: clinical and genomic evaluation, J. Kidney Cancer VHL. 7 (1) (2020) 7–11.
[72] T Tran, C Blanc, C Granier, A Saldmann, C Tanchot, E. Tartour, Therapeutic cancer vaccine: building the future from lessons of the past, Semin. Immunopathol. 41 (1) (2019) 69–85.
[73] MG Sönmez, LÖ. Sönmez, New treatment modalities with vaccine therapy in renal cell carcinoma, Urol. Ann. 11 (2) (2019) 119–125. -.
[74] J Sundblom, TP Skare, O Holm, S Welin, M Braun, P Nilsson, P Enblad, EO Sjöström, A. Smits, Central nervous system hemangioblastomas in von Hippel-Lindau disease: total growth rate and risk of developing new lesions not associated with circulating VEGF levels, PLoS ONE 17 (11) (2022) e0278166.
[75] FW Meng, FS Liu, WH Liu, L Li, LL. Jie, Formation of new lymphatic vessels in glioma: an immunohistochemical analysis, Neuropathology. 40 (3) (2020) 215–223.
[76] S De Biasi, L Gibellini, A Feletti, G Pavesi, E Bianchini, D Lo Tartaro, S Pecorini, A De Gaetano, R Pullano, F Boraldi, M Nasi, M Pinti, A Cossarizza, High speed flow cytometry allows the detection of circulating endothelial cells in hemangioblastoma patients, Methods 134-135 (2018) 3–10.
[77] E Pilotto, G Midena, T Torresin, G De Mojà, ML Bacelle, AM Ferrara, S Zovato, E. Midena, Retinal glial cells in Von Hippel-Lindau disease: a novel approach in the pathophysiology of retinal hemangioblastoma, Cancers 14 (1) (2021) 170.
[78] M Chrabańska, M Rynkiewicz, P Kiczmer, B. Drozdzowska, Immunohistochemical expression of CD44, MMP-2, MMP-9, and Ki-67 as the prognostic markers in non-clear cell renal cell carcinomas-a prospective cohort study, J. Clin. Med. 11 (17) (2022) 5196.
[79] B Odom, I Khourdaji, V Golas, R Zekman, B. Rosenberg, Acquired von Willebrand Disease Secondary to Clear Cell Renal Cell Carcinoma, J. Endourol. Case Rep. 4 (1) (2018) 114–116.
[80] R Bílek, P Vlček, L Šafařík, D Michalský, K Novák, J Dušková, E Václavíková, J Widimský Jr, T Zelinka, Chromogranin A in the laboratory diagnosis of pheochromocytoma and paraganglioma, Cancers 11 (4) (2019) 586.
[81] J Ahn, JY Park, G Kim, SM Jin, KY Hur, SY Lee, JH. Kim, Urinary free metanephrines for diagnosis of pheochromocytoma and paraganglioma, Endocrinol. Metab. 36 (3) (2021) 697–701.
[82] R Garcia-Carbonero, B Anton-Pascual, A Modrego, M Del Carmen Riesco-Martinez, A Lens-Pardo, C Carretero-Puche, B Rubio-Cuesta, B Soldevilla, Advances in the treatment of gastroenteropancreatic neuroendocrine carcinomas: are we moving forward? Endocr. Rev. 44 (4) (2023) 724–736.
[83] S Faias, S Prazeres, M Cunha, L Pereira, R Roque, P Chaves, M Cravo, I Claro, M Silveira, V Leite, A. Dias Pereira, Chromogranin A and NSE in cystic pancreatic neuroendocrine tumors, Clin. Res. Hepatol. Gastroenterol. 45 (4) (2021) 101601.
[84] F Greco, V D'Andrea, B Beomonte Zobel, CA Mallio, Radiogenomics and texture analysis to detect von Hippel-Lindau (VHL) mutation in clear cell renal cell carcinoma, curr Issues Mol Biol. 46 (4) (2024) 3236–3250.
[85] C Suárez, M Vieito, A Valdivia, M González, J. Carles, Selective HIF2A inhibitors in the management of clear cell renal cancer and Von Hippel-Lindau-disease-associated tumors, Med. Sci. 11 (3) (2023) 46.
[86] L Incorvaia, G Badalamenti, V Gristina, A Galvano, A Russo, DG Iacopino, M Silvestrini, V Bazan, F Brighina, V. Di Stefano, Immunological aspects of Von Hippel-Lindau disease: a focus on neuro-oncology and myasthenia gravis, Diagnostics 13 (1) (2023) 144.
[87] TK Choueiri, WG Kaelin Jr., Targeting the HIF2-VEGF axis in renal cell carcinoma, Nat. Med. 26 (10) (2020) 1519–1530.
[88] X Fan, S Wang, T Chen, W Hu, H. Yang, Von-Hipple Lindau syndrome with family history: a case report and seventeen years follow-up study, Front. Oncol. 14 (2024) 1360942.
[89] M Lian, M Mortoglou, P. Uysal-Onganer, Impact of hypoxia-induced miR-210 on pancreatic cancer, Curr. Issues Mol. Biol. 45 (12) (2023) 9778–9792.
[90] LM Cardenas, JE Deluce, S Khan, O Gulam, S Maleki Vareki, R Fernandes, AA Lalani, Next wave of targets in the treatment of advanced renal cell carcinoma, Curr. Oncol. 29 (8) (2022) 5426–5441.
[91] HE Wiley, V Krivosic, A Gaudric, MB Gorin, C Shields, J Shields, ME Aronow, EY. Chew, Management of retinal hemangioblastoma in Von Hippel-Lindau disease, Retina 39 (12) (2019) 2254–2263.
[92] ER. Maher, Hereditary renal cell carcinoma syndromes: diagnosis, surveillance and management, World J. Urol. 36 (12) (2018) 1891–1898.
[93] S Laks, R van Leeuwaarde, D Patel, XM Keutgen, P Hammel, N Nilubol, TP Links, TR Halfdanarson, AB Daniels, A Tirosh, Pancreatic Manifestations Recommendations Development Subcommittee of the VHL Alliance. Management recommendations for pancreatic manifestations of von Hippel-Lindau disease, Cancer 128 (3) (2022) 435–446.
[94] M Louise, M Binderup, M Smerdel, L Borgwadt, SS Beck Nielsen, MG Madsen, HU Møller, JF Kiilgaard, L Friis-Hansen, V Harbud, S Cortnum, H Owen, S Gimsing, HA Friis Juhl, S Munthe, M Geilswijk, ÅK Rasmussen, U Møldrup, O Graumann, F Donskov, H Grønbæk, B Stausbøl-Grøn, O Schaffalitzky de Muckadell, U Knigge, G Dam, KA Wadt, L Bøgeskov, P Bagi, L Lund, K Stochholm, LB Ousager, Sunde L. von, Hippel-Lindau disease: updated guideline for diagnosis and surveillance, Eur. J. Med. Genet. 65 (8) (2022) 104538.
[95] U Capitanio, G Rosiello, S Erdem, I Rowe, O Kara, E Roussel, R Campi, T Klatte, MC Kriegmair, M Sibona, R Bertolo, I Ouzaid, MC Mir, G Marra, A Larcher, F Montorsi, A Salonia, Kidney Cancer Working Group of the Young Academic Urologists (YAU) Working Party of the European Association of Urology (EAU). Clinical, surgical, pathological and follow-up features of kidney cancer patients with Von Hippel-Lindau syndrome: novel insights from a large consortium, World J. Urol. 39 (8) (2021) 2969–2975.