

STF31 Targeting GLUT1 in VHL-Deficient Clear Cell Renal Cell Carcinoma

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Abstract

VHL gene is a typical gene that is frequently mutated in clear cell renal cell carcinoma (ccRCC). It can promote the expression of glucose transporter 1 (GLUT1) and the Warburg effect by stabilizing hypoxia-inducible factor 1 α (HIF-1 α) to induce glycolytic dependence in tumour cells. Targeted Therapy to address the metabolic weakness can also be used. Systematically review the metabolic regulatory mechanism of HIF-1 α /GLUT1 in VHL-inactivation and summarize the anti-tumour effects and potential applications of the selective GLUT1 inhibitor STF-31. Studies have shown that VHL dysfunction leads to the continuous accumulation of HIF-1 α , which upregulates GLUT1 and glycolysis-related genes, thus promoting a state of persistent aerobic glycolysis in ccRCC cells. High expression of GLUT1 is associated with enhanced tumour invasion and a poor prognosis.

STF-31 can selectively inhibit GLUT1-mediated glucose uptake to cause energy metabolism disorders, and it preferentially inhibits VHL-deficient tumour cells via synthetic lethality. Previous in vitro and animal studies have also shown that STF-31 is good at inhibiting cancer and is relatively non-toxic to normal cells. The metabolic axis of VHL-HIF-1 α -GLUT1 is a potential therapeutic target for ccRCC, and STF-31 has proposed a new research direction in metabolic-targeted therapy of VHL-deficient tumours. In the future, research will be conducted to further optimise the pharmacokinetics and drug-delivery properties of STF-31, explore combination strategies with immunotherapy and anti-angiogenic therapy, and carry out clinical trials to evaluate its efficacy and safety in patients before use in patients.

Key words

Clear cell renal cell carcinoma; VHL; GLUT1; STF31; Warburg effect.

1. Introduction

Von Hippel-Lindau (VHL) gene loss-of-function

mutations are the main causative factors for clear cell renal cell carcinoma (ccRCC), and they are also associated with several other rare malignant tumours, such

as hemangioblastoma and pancreatic neuroendocrine tumours [1]. Wild-type VHL protein serves as a substrate-recognition component of the E3 ubiquitin ligase complex to facilitate ubiquitination and proteasomal degradation of hypoxia-inducible factor 1 α (HIF-1 α) [1]. Once VHL is deleted or inactivated, HIF-1 α cannot be cleared and accumulates continuously inside tumor cells under normoxic conditions [1]. Stabilised HIF-1 α functions as a master transcription factor that promotes the expression of many genes involved in angiogenesis, cell proliferation and glucose metabolism [2]. Among the target genes, solute carrier family 2 member 1 (SLC2A1), which encodes glucose transporter 1 (GLUT1), is significantly upregulated in VHL-deficient tumour cells [2]. Numerous GLUT1 transporters are located on the cell membrane, enhancing glucose uptake to drive prolonged aerobic glycolysis; this is known as the Warburg effect [2]. Different from normal somatic cells that are primarily powered by mitochondrial oxidative phosphorylation, VHL-mutant cancer cells under aerobic conditions have switched to glycolysis and generate a large amount of lactate to support rapid biomass production and malignancy [2]. Clinically, high expression of GLUT1 and enhanced glycolytic flux have been repeatedly confirmed as biomarkers for advanced stage, metastasis and poor overall survival in ccRCC patients [3]. Current standard therapies for VHL-deficient renal cell carcinoma include anti-VEGF angiogenesis inhibitors, mTOR inhibitors and immune checkpoint inhibitors. However, a relatively large number of patients develop primary or acquired drug resistance, and these regimens cannot directly target the core metabolic vulnerability caused by VHL loss [3]. Therefore, the development of glycolysis-targeting small molecules to inhibit the Warburg effect has become a promising direction for personalised therapy in this patient group [3]. STF-31 is a synthetic selective small-molecule inhibitor of GLUT1 that, unlike non-specific glycolytic inhibitors such as 2-DG, selectively binds to GLUT1 to block transmembrane glucose transport and does not severely affect glucose uptake in healthy tissues [4]. A series of preclinical studies have confirmed that STF-31 exhibits strong synthetic lethal cytotoxicity in VHL-deficient tumour cells by inhibiting glucose-dependent energy metabolism, and only mild systemic toxicity was observed in animals [4].

Systematically explore the molecular pathway of VHL loss, HIF-1 α stabilisation and GLUT1 upregulation that leads to the Warburg effect. This paper will introduce the chemical properties and molecular mechanisms of STF-31, demonstrate its preclinical anti-tumour effects, propose a reasonable combination therapy plan to enhance the anti-tumour efficacy, and examine pharmacokinetic and translational problems that restrict its clinical application. Finally, this paper proposes new research ideas to improve STF-31 and extend its application in clinical practice, providing a theoretical basis for the development of metabolic-targeted therapy for VHL-mutated malignant tumours.

2. Molecular Basis of Warburg Effect in VHL-Deficient Tumors

Clear cell renal cell carcinoma (ccRCC) frequently presents with biallelic inactivation of the VHL tumour suppressor gene, which is often the initial genetic change in around 75%-90% of sporadic ccRCC cases [5,6]. Loss of functional pVHL triggers constitutive activation of hypoxia-inducible factor (HIF) signalling under normoxic conditions, a state termed pseudohypoxia. The above-mentioned abnormal signalling cascade has rearranged central carbon metabolism and promoted the occurrence of the Warburg effect, i.e., oxygen-independent glycolysis in the presence of oxygen. Systematically analyze the molecular pathway that connects VHL loss to glycolytic metabolic addiction in this section, and focus on HIF-1 α -dependent transcriptional upregulation of GLUT1 as a key effector node.

2.1 Physiological function of wild-type VHL protein

The human VHL gene codes for von Hippel-Lindau protein (pVHL), a multifunctional tumour suppressor expressed ubiquitously in mammalian tissues, and has two main isoforms (pVHL30 and pVHL19) generated by alternative translation initiation [7,8]. The canonical physiological activity of wild-type pVHL requires it to function as the substrate recognition subunit of the VBC (VHL-Elongin B-Elongin C) E3 ubiquitin ligase complex, which is assembled with Elongin B, Elongin

C, Cullin2 (CUL2) and RING-box protein 1 (RBX1) [6]. Under normoxia, the VBC E3 ligase keeps oxygen homeostatically regulated by inducing proteasomal degradation of HIF-1 α . In oxygen-rich environments, PHDs hydroxylate conserved proline residues on HIF-1 α ; these hydroxylated sites bind to the beta-domain of pVHL and promote ubiquitination and degradation of HIF-1 α , thus repressing hypoxia-responsive gene transcription. VHL inactivation disrupts this oxygen-sensing pathway, leading to prolonged accumulation of HIF-1 α and continuous promotion of glycolysis in ccRCC. Structurally, pVHL has two conserved regions: the α -domain binds to Elongin B/C to recruit the other components of the ligase complex, and the β -domain recognizes hydroxylated substrate motifs for ubiquitination.

The first target of the VBC complex in terms of physiology is the α -subunit of hypoxia-inducible factors (HIF-1 α and HIF-2 α), which regulate gene expression under low-oxygen conditions. Under normoxic conditions, iron- and oxygen-dependent prolyl hydroxylase domain enzymes (PHD1/2/3) catalyze proline hydroxylation in the oxygen-dependent degradation domain (ODD) of HIF- α proteins. This post-translational modification creates a high-affinity binding epitope for the β -domain of pVHL. After recognition, the VBC complex catalyzes K48-linked polyubiquitination of HIF- α , thus targeting this transcription factor for rapid proteasomal degradation and keeping basal levels of HIF- α in well-oxygenated cells extremely low [4].

In addition to regulating HIF, the wild-type pVHL also serves in the homeostasis of the extracellular matrix, cell-cycle regulation and mTOR signalling. However, the tumour-suppressive effect of pVHL is mainly achieved by suppressing HIF accumulation, and the reintroduction of wild-type, but not tumour-derived mutant pVHL, restores HIF- α turnover and inhibits tumour formation in VHL-deficient renal cell carcinoma xenograft models [7].

2.2 Consequence of VHL gene inactivation: HIF-1 α stabilization

Biallelic inactivation of the VHL gene occurs through somatic mutation, chromosomal loss or promoter hypermethylation in sporadic ccRCC, and germline heterozygous VHL mutation causes hereditary von

Hippel-Lindau disease; in both cases, loss of functional pVHL prevents substrate recognition by the VBC complex and ubiquitination machinery [8,9]. Most oncogenic VHL mutations disrupt the substrate-binding β -domain or the α -domain involved in complex assembly, and thus cannot bind hydroxylated HIF- α proteins.

Note that ccRCC has context-dependent functional divergence of HIF-1 α and HIF-2 α . HIF-2 α is a well-known oncogene in many subsets of ccRCC, and HIF-1 α also has multiple functions that promote tumour growth. However, HIF-1 α is still required to organise the transcriptional reprogramming of glycolysis and directly induces glucose transporters and glycolytic enzymes. Single-cell and bulk transcriptomic data also show that HIF-1 α is frequently co-stabilised with HIF-2 α in primary VHL-mutant ccRCC tumours and together regulate metabolic programmes [10].

2.3 HIF-1 α -mediated Transcriptional Upregulation of GLUT1

Nuclear HIF-1 α /HIF-1 β heterodimers bind to conserved hypoxia response elements (HREs; consensus sequence 5'-RCGTG-3') located in the promoter and enhancer regions of hundreds of target genes that regulate metabolism, angiogenesis, cell survival and proliferation. SLC2A1, which codes for glucose transporter 1 (GLUT1), is a direct and well-validated transcriptional target of HIF-1 α [9]. GLUT1 is a type of integral membrane protein that facilitates the transport of glucose across the cell membrane. Chromatin immunoprecipitation (ChIP) assays show that HIF-1 α directly binds to multiple HRE sites upstream of the SLC2A1 transcription start site. Upon binding of HIF-1 α , coactivators such as p300/CBP are recruited to restructure the local chromatin environment and promote the transcription of SLC2A1 and the expression of membrane-bound GLUT1 protein [10].

In VHL-deficient ccRCC models, genetic restoration of wild-type pVHL reduces HIF-1 α levels and significantly suppresses GLUT1 expression; conversely, forcing the stabilisation of HIF-1 α in VHL-proficient tubular epithelial cells is sufficient to replicate the high GLUT1 and increased glucose consumption phenotype. GLUT1 upregulation removes glucose availability as a rate-limiting step and increases the speed of glycolysis.

HIF-1 α promotes a coordinated transcriptional program of glycolysis that includes hexokinase 2 (HK2), lactate dehydrogenase A (LDHA), and pyruvate dehydrogenase kinase 1 (PDK1); thus, it drives the conversion towards lactate production rather than mitochondrial oxidative phosphorylation [11].

2.4 Metabolic Rewiring: Persistent Aerobic Glycolysis as Tumor Survival Dependency

The accumulated transcriptional products of stabilised HIF-1 α promote whole-cell metabolic reprogramming and thus induce the Warburg effect in VHL-deficient tumour cells. Increased GLUT1 expression enhances glucose uptake by the cell; subsequently, HIF target genes divert glucose carbon away from mitochondrial TCA cycle oxidation. PDK1 phosphorylates and inhibits pyruvate dehydrogenase (PDH), prevents the conversion of pyruvate to acetyl-CoA, and suppresses oxidative phosphorylation. At the same time, LDHA reduces pyruvate to lactate and thus regenerates cytosolic NAD⁺ to keep glycolysis running under normoxia [9].

Aerobic glycolysis has a relatively low ATP yield per glucose molecule compared to complete mitochondrial oxidation but is suitable for anabolic proliferation. Glycolytic intermediates are distributed to all sites of branching biosynthesis; for example, the pentose phosphate pathway provides precursors for nucleotide synthesis and serine biosynthesis for amino acid production to rapidly divide tumour cells. VHL-mutant ccRCC shows this glycolytic phenotype due to the oncogenic signal, but it has become necessary for life rather than being a mere side effect. Pharmacological or genetic inhibition of GLUT1 severely reduces glucose uptake, suppresses glycolytic flux, causes energy stress and induces apoptosis in VHL-deficient RCC cell lines, and has little toxicity in VHL-proficient renal epithelial cells [12].

Lactate is exported by monocarboxylate transporters, lowers the extracellular pH of the tumour microenvironment, and thus promotes invasion, immune evasion and therapeutic resistance. In addition, the addition of wild-type pVHL alters the Warburg effect by promoting oxidative phosphorylation and reducing lactate production; thus, it can be inferred that VHL functions to regu-

late this metabolic switch [13].

2.5 Clinical evidence: GLUT1 Overexpression Correlates with Poor Prognosis in VHL-deficient ccRCC

Preclinical mechanistic data have been confirmed by multiple independent clinical cohort studies to show that GLUT1 overexpression is a prognostic marker for ccRCC, the representative VHL-deficient human malignancy. Immunohistochemical and transcriptomic analyses have consistently shown that primary ccRCC lesions have significantly higher levels of GLUT1 protein and mRNA compared with normal renal cortex tissue, and GLUT1 expression is strongly associated with underlying VHL mutation status and intratumoral HIF-1 α activity [14].

GLUT1 expression is positively correlated with severe pathological features in patients, such as high Fuhrman nuclear grade, large tumour size, venous invasion and tumour necrosis. Survival analysis of a retrospective cohort shows that patients with high GLUT1 expression have a significantly shorter overall survival and cancer-specific death rate compared with those having low GLUT1 expression, after controlling for clinical factors such as tumour stage and grade [14].

GLUT1 abundance determines the intensity of ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) uptake in functional imaging studies via positron emission tomography (PET). High FDG avidity of ccRCC lesions indicates increased glycolysis and is associated with metastasis. Stratified analysis further shows that the prognostic effect of GLUT1 is most prominent in tumours with confirmed biallelic VHL inactivation, thus strengthening the causal chain: VHL loss $\rightarrow$ HIF-1 α stabilisation $\rightarrow$ GLUT1 upregulation $\rightarrow$ enhanced glycolysis $\rightarrow$ aggressive tumour behaviour [14].

In short, clinical observations have confirmed the translation of the molecular cascade mentioned above. GLUT1 and the Warburg effect are the results of disrupted VHL/HIF regulation and can be targeted for treatment. At present, preclinical studies are investigating GLUT1 inhibitors and glycolysis-targeted drugs in combination therapy for advanced ccRCC resistant to standard anti-angiogenic treatment.

3. STF-31: A Selective Small-Molecule GLUT1 Inhibitor

3.1 Discovery, chemical characteristics and GLUT1 binding mechanism of STF-31

STF-31 is a specific small-molecule inhibitor of GLUT1 that was identified by high-throughput screening of a chemical library and induced synthetic lethality in VHL-deficient ccRCC [15]. The design rationale for this screen was based on the oncogenic cascade activated by VHL loss: without pVHL, HIF-1 α is stabilized and thus upregulated transcriptionally; consequently, tumour cells in ccRCC exhibit a high degree of dependence on GLUT1-mediated glucose uptake for survival. Chemically, STF-31 is a sulfonamide derivative with a stable molecular structure that effectively binds to GLUT1 and inhibits glucose transport. It was first identified as selectively cytotoxic to VHL-null RCC cells, and thus targeted glycolysis therapy in ccRCC was developed [16].

Molecular docking and functional experiments show that STF-31 directly targets the central transport pathway of the GLUT1 transmembrane protein [16]. STF-31 forms stable hydrogen bonds with the key amino acid residues Arg126 and Trp388 in the GLUT1 pore domain. This bond blocks the transmembrane glucose-transport pathway and thus inhibits GLUT1-mediated glucose uptake, reducing the concentration of glucose in tumour cells rapidly [15].

3.2 Selective Metabolic Inhibition and Synthetic Lethal Anti-Tumor Pathway of STF-31

STF-31 has excellent tissue selectivity and is therefore relatively superior. Normal renal epithelial cells mainly express GLUT2 and are powered by mitochondrial oxidative phosphorylation; they do not use GLUT1-dependent aerobic glycolysis [17]. STF-31 has little inhibitory effect on GLUT2 and other ubiquitous glucose transporters, thus showing low cytotoxicity to normal renal cells. VHL-deficient ccRCC cells are highly dependent on GLUT1 overexpression and are there-

fore uniquely sensitive to STF-31 inhibition [15].

STF-31 is selectively lethal to VHL-deficient ccRCC by inhibiting glycolysis. VHL loss-driven HIF-1 α hyperactivation locks tumour cells in a GLUT1-dependent glycolytic state and causes metabolic inflexibility [18]. STF-31 treatment reduces glucose uptake to a certain extent, inhibits glycolysis, causes a decrease in ATP levels, and thus induces tumour cell apoptosis and necrosis [16]. Selectively inhibit metabolism to suppress tumour growth in vivo without damaging normal tissues, and thus STF-31 has been identified as a highly specific treatment for VHL-deficient ccRCC [17].

4. Preclinical Antitumor Activity of STF-31 Against VHL-Deficient Tumors

4.1 In Vitro Cellular Experiments: Proliferation Arrest, Apoptosis Induction

In vitro cellular assays show that STF-31 has selective anti-proliferative activity for VHL-null ccRCC cell lines only, and wild-type VHL renal cells are largely unaffected [18]; dose-gradient STF-31 treatment inhibits glucose uptake, stops cell cycle progression in the G1 phase, and significantly reduces colony formation ability. Terminal deoxynucleotidyl transferase staining and flow cytometry verify strong apoptosis activation: when deprived of glycolytic substrates, tumour cells upregulate cleaved caspase-3 and pro-apoptotic Bax, whereas normal renal tubular cells maintain normal energy metabolism and evade cell death [19].

4.2 In Vivo PDX/Xenograft Models: Single-Agent Tumor Regression Effect

Subcutaneous xenograft and patient-derived xenograft (PDX) models have reproduced the therapeutic effect of STF-31 as a monotherapy. Oral administration of STF-31 yields sustained reduction in tumour volume of VHL-deficient ccRCC xenografts, with over 50% tumour weight loss after 21 consecutive doses [18], and PDX models derived from human clear cell renal carcinoma further confirm consistent tumour growth suppression and translational potential of GLUT1 inhibition for

clinical treatment [20].

4.3 Biomarker Changes: Glycolytic Gene Expression, Lactate Production, ATP Level

Mechanistic biomarker analysis has identified metabolic suppression induced by STF-31; qPCR results show that HIF-1 α , GLUT1, HK2 and LDHA in the treated tumour tissue were downregulated [4]. Metabolite analysis shows that the intracellular lactate is reduced and ATP is severely depleted. These metabolic changes are not present in the adjacent normal kidney tissue, and STF-31 specifically disrupts the Warburg effect of VHL-deficient tumours [19].

4.4 Toxicity Profile of STF-31 in Animal Models

STF-31 has a good safety profile in murine preclinical models. Continuous daily administration has not resulted in weight loss of the mice, damage to the liver or kidneys, or alterations in blood counts. Histopathological examination of the major visceral organs shows no obvious damage, and this is due to STF-31's low affinity for GLUT2/GLUT4 transporters in normal organs [18]. STF-31 has minimal off-target toxicity compared with pan-glycolytic inhibitors and is therefore suitable for extended targeted metabolic therapy.

5. Conclusion

Systematically reveal the entire molecular pathway that connects VHL inactivation, HIF-1 α hyperactivation, GLUT1 overexpression and Warburg metabolic reprogramming in ccRCC, and confirm the preclinical therapeutic effect of the selective GLUT1 inhibitor STF-31. Loss of functional pVHL prevents the oxygen-dependent degradation of HIF-1 α , continuously increases transcription of GLUT1 and other glycolytic genes, and thus alters tumour metabolism into an irreversible aerobic glycolysis-dependent state. GLUT1 overexpression is a good prognostic factor for an aggressive tumour in clinical practice, and thus belongs to the cluster of metabolic alterations discussed here. STF-31 is a high-selectivity GLUT1 inhibitor that blocks glucose supply

and glycolytic flux in VHL-deficient tumour cells, thus inducing energy depletion and tumour cell apoptosis through synthetic lethality. Based on the preclinical in vitro and in vivo studies, STF-31 has inhibited the proliferation of ccRCC without harm to normal cells, and there is minimal inhibition of normal glucose transporters. Collectively, this work shows that the VHL-HIF-1 α -GLUT1 metabolic axis is a key therapeutic vulnerability in ccRCC, and STF-31 is a promising and safe targeted agent for future clinical translation and adjuvant therapy development of VHL-deficient ccRCC.

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