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Current Research Status of ATP6V Gene Family in Human Cancers

Yazhou Yang[1,2], Jun Tang[1*]

[1]Department of Gastrointestinal Surgery, The Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, China
[2]School of Clinical Medicine, Youjiang Medical University for Nationalities, Baise, China
Email: *tangj202508@163.com

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Abstract

Vacuolar H^+-ATPase (V-ATPase), encoded by the ATP6V gene family, is an evolutionarily conserved, a multisubunit proton pump that plays a fundamental role in maintaining intracellular pH homeostasis, ion balance, and lysosomal function. Increasing evidence indicates that dysregulation of V-ATPase expression and activity is closely associated with tumorigenesis and cancer progression. V-ATPase mediates ATP-dependent proton transport across membranes, thereby acidifying various intracellular compartments such as lysosomes, endosomes, the Golgi apparatus, and secretory vesicles, which is essential for protein degradation, trafficking, and autophagy. Beyond its canonical roles, V-ATPase has been shown to participate in multiple oncogenic signaling pathways, including mTORC1 and Wnt/β-catenin, thereby modulating cellular metabolism, proliferation, and survival. Notably, overexpression of V-ATPase in cancer cells contributes to the acidification of the extracellular microenvironment, facilitating invasion, metastasis, and resistance to therapy. This review summarizes current advances in the understanding of ATP6V family genes and V-ATPase function in cancer biology, highlighting their potential as diagnostic biomarkers and therapeutic targets.

Keywords

ATP6V Gene Family, Malignant Tumors, V-ATPase, Function, Signaling Pathways

1. Introduction

Vacuolar H^+-ATPase (V-ATPase) is a highly conserved, ATP-dependent proton pump composed of multiple subunits organized into two distinct domains: the peripheral V_1 domain, responsible for ATP hydrolysis, and the membrane-inte-

grated V_0 domain, which mediates proton translocation [1]. Together, these domains consist of at least 14 core subunits, along with accessory proteins such as ATP6AP1 and ATP6AP2. V-ATPase plays a fundamental role in maintaining intracellular and organelle pH homeostasis, supporting essential physiological processes such as protein degradation, membrane trafficking, autophagy, and endosomal acidification. Beyond its canonical role in cellular physiology, V-ATPase has been increasingly recognized for its contribution to tumor progression [2]. In cancer cells, V-ATPase activity is often upregulated, facilitating an acidic tumor microenvironment (TME) that promotes cancer cell proliferation, invasion, and metastasis [3]. The acidic extracellular pH—typically ranging from 6.5 to 6.9 or even lower—is now considered a hallmark of malignancy. This acidification is driven by multiple pathological processes, including metabolic reprogramming (e.g., the Warburg effect), enhanced proton extrusion, and abnormal tumor-associated vasculature [4]. Specifically, oncogenic mutations enhance glycolytic flux, resulting in excessive lactate production and H^+ accumulation, which collectively lower the local extracellular pH. The resulting acidic TME supports tumor growth and survival by degrading the extracellular matrix, activating invasion-related signaling (e.g., MMPs and HIF-1*α*), suppressing immune cell activity, and promoting resistance to chemotherapy and immunotherapy [5].

At the molecular level, the subunits of V-ATPase are encoded by the ATP6V gene family. Recent studies have demonstrated that several ATP6V genes—such as ATP6V1A, ATP6V0D1, and ATP6V1C1—are significantly overexpressed in various cancers, including breast, liver, and prostate malignancies. These subunits contribute to cancer progression by modulating the acidic TME, enhancing glycolysis, maintaining cancer stem cell properties, mediating immune escape, and driving therapy resistance. Moreover, ATP6V-mediated acidification facilitates positive feedback interactions with enzymes like lactate dehydrogenase A (LDHA), further promoting tumorigenic metabolic loops [6]. Targeting ATP6V function through pharmacological inhibitors (e.g., bafilomycin A1) or gene silencing has shown promise in preclinical studies by reversing drug resistance and enhancing immunotherapy efficacy [7]. However, challenges such as subunit-specific targeting and systemic toxicity remain significant barriers. Collectively, these findings highlight the ATP6V gene family as a novel class of prognostic biomarkers and therapeutic targets, offering new opportunities for precision oncology.

2. ATP6V Gene Family

The ATP6V gene family encodes the subunits of vacuolar H^+-ATPase (V-ATPase), an evolutionarily conserved transmembrane proton pump that regulates organelle acidification and cellular microenvironment homeostasis through coordinated action of its two functional domains, V_1 and V_0. The cytoplasmic V_1 domain, comprising subunits such as ATP6V1A, ATP6V1B1, ATP6V1B2, ATP6V1C1, ATP6V1C2, ATP6V1D, ATP6V1E1, ATP6V1E2, ATP6V1F, ATP6V1G1, ATP6V1G2, ATP6V1G3, and ATP6V1H, hydrolyzes ATP to generate mechanical

energy. Meanwhile, the membrane-embedded V_0 domain, which includes ATP6V0A1, ATP6V0A2, ATP6V0A4, ATP6V0B, ATP6V0C, ATP6V0D1, ATP6V0D2, ATP6V0E1, and TCIRG1, mediates proton translocation across membranes. This dual-domain architecture enables V-ATPase to maintain intracellular and extracellular pH gradients, thereby influencing cellular metabolism and signal transduction. Genomic analyses reveal that ATP6V family members are distributed across multiple chromosomes, with several paralogs (e.g., ATP6V1B2, ATP6V1C1, ATP6V1H, ATP6V0D2) exhibiting tissue- and organelle-specific expression patterns to meet diverse physiological demands [8].

The ATP6V gene family encodes the V-ATPase complex, a critical transmembrane proton pump responsible for intracellular proton transport, with multifaceted roles in both physiological and pathological contexts. Powered by ATP hydrolysis, V-ATPase acidifies intracellular compartments and regulates microenvironmental pH homeostasis, with compartment-specific functions. Within the endocytic pathway, it maintains acidification of endosomes, lysosomes, and secretory vesicles, thereby mediating processes such as endocytosis, pathogen entry, and neurotransmitter release. In specialized tissues, V-ATPase regulates systemic acid-base balance and mineral metabolism; for instance, it contributes to proton secretion in renal tubules and bone resorption in osteoclasts, the latter highlighting its potential as a therapeutic target in osteoporosis. In cancer cells, V-ATPase-driven acidification of the tumor microenvironment leads to reversal of intracellular drug concentration gradients—exemplified by reduced intracellular accumulation of chemotherapeutic agents like doxorubicin—while simultaneously activating lysosomal hydrolases and matrix metalloproteinases (MMPs) that degrade the extracellular matrix, facilitating tumor invasion and metastasis. Experimental evidence supports that targeted inhibition of key ATP6V subunits can reverse drug resistance and suppress tumor progression, underscoring the therapeutic potential of ATP6V as a novel anti-cancer target [9].

3. Genetic Variations in ATP6V Gene Family

Genetic mutations refer to heritable alterations in the DNA sequence that can disrupt protein-coding regions or regulatory elements, thereby leading to functional abnormalities and phenotypic consequences. Such mutations may occur in germline cells, enabling inheritance, or in somatic cells, contributing to tumorigenesis. As an essential proton pump located on membranes of various intracellular organelles and the plasma membrane, mutations in V-ATPase impair its core proton transport function, resulting in tissue-specific pathological effects. The underlying mechanisms involve defects in structural assembly, ionic homeostasis, and cellular microenvironment regulation [10]. Mutations in ATP6V genes disrupt proton pump activity and are implicated in a spectrum of diseases. Structural mutations, such as missense variants in ATP6V1B1 and ATP6V0A4, lead to subunit assembly defects or impaired proton translocation [11]. Functional deficiencies manifest as disturbed pH homeostasis, leading to

lysosomal storage disorders (e.g., ATP6V0A2 mutations causing cutis laxa) or renal tubular acidosis (e.g., ATP6V1B1 mutations) [12]. Tissue-specific effects are observed in osteoclast mutations of ATP6V0D2, resulting in osteopetrosis, and in inner ear mutations linked to sensorineural deafness [13]. In oncology, overexpression of ATP6V0C promotes tumor metastasis by acidifying the microenvironment, while upregulation of ATP6V family genes contributes to lysosomal drug sequestration and chemoresistance [14]. These genetic alterations interfere with proton transport, organelle acidification, and critical signaling pathways such as mTOR, thereby affecting bone resorption, tumor progression, and other physiological processes. Consequently, ATP6V mutations represent promising targets for the treatment of hereditary disorders, bone diseases, and cancers.

4. Post-Translational Modifications of ATP6V Gene Family

The activity, localization, and stability of proteins encoded by the ATP6V gene family are tightly regulated by a variety of post-translational modifications (PTMs), which play crucial roles in cellular metabolism, membrane trafficking, and the pathogenesis of diseases such as cancer and neurodegenerative disorders. Unlike transcriptional or translational regulation, PTMs directly modulate protein function by covalently attaching chemical groups to amino acid residues. Among these modifications, ubiquitination—mediated by the attachment of a 76-amino acid ubiquitin molecule—regulates key biological processes such as transcription factor stability, chromatin remodeling, and Wnt/β-catenin signaling [15]. For V-ATPase, several types of PTMs have been implicated in functional regulation: 1) Phosphorylation modulates enzymatic activity and is involved in bone resorption and tumor microenvironment acidification [16]; 2) Ubiquitination controls protein degradation and is associated with neurodegenerative diseases and chemoresistance in cancers [17]; 3) Acetylation influences subunit assembly and cellular energy metabolism [16]; 4) Glycosylation affects membrane localization, with defects leading to lysosomal storage disorders [18]; 5) Oxidative modifications, often induced by reactive oxygen species (ROS), can reversibly inhibit V-ATPase activity [19]. These PTMs orchestrate the dynamic regulation of V-ATPase function, contributing to bone remodeling, cancer progression, and neuronal degeneration. Consequently, targeting specific PTMs offers promising therapeutic strategies for related disorders.

5. Expression Patterns and Functional Heterogeneity of ATP6V Family Genes in Various Cancers

Based on analyses from the TCGA database, ATP6V family genes are significantly upregulated in multiple malignancies, including ovarian cancer, hepatocellular carcinoma, colorectal cancer, and clear cell renal cell carcinoma. These genes contribute to tumorigenesis, progression, and therapeutic resistance through diverse molecular mechanisms. Subunits of the ATP6V family demonstrate notable func-

tional heterogeneity across different cancers. For example, in clear cell renal cell carcinoma, ATP6V0D2 inhibits angiogenesis and reduces sunitinib resistance by promoting the autophagic degradation of EPAS1/HIF-2α [20]. In hepatocellular carcinoma, ATP6V1D-mediated lysosomal acidification supports cancer stem cell properties through a biphasic regulatory mechanism [21]. ATP6V1B1 regulates malignancy progression and cisplatin sensitivity in renal cancer via the mTOR/autophagy signaling axis [22]. In colorectal cancer, high expression of ATP6V1C2 promotes metastasis and poor prognosis by activating Wnt downstream targets such as c-Myc and Cyclin D1 [23].

Moreover, dysfunction of ATP6V0A2 disrupts Golgi ion homeostasis and impairs spermatogenesis, while ATP6V1G1 contributes to hepatocarcinogenesis through phosphorylation-dependent networks [24] [25]. Of particular note, ATP6V1C1, a key regulator of mTORC1, also impacts the tumor immune microenvironment, and prosapogenin. A disrupts lysosomal function by upregulating ATP6V1A and ATP6V1B2, suggesting potential therapeutic implications [26] [27]. These findings highlight the roles of ATP6V subunits in regulating lysosomal acidification, autophagy, signaling pathways, and tumor microenvironment, providing novel insights into targeted therapy development. In summary, ATP6V subunits display highly heterogeneous expression patterns and functional roles across different cancer types. To provide a clearer overview, we compiled the expression trends and associated signaling pathways of major ATP6V subunits in human cancers (**Table 1**), highlighting their functional diversity and potential therapeutic implications.

Table 1. Expression trends and functional roles of ATP6V subunits in major cancers.

Subunit	Expression trend in major cancers	Key pathways/mechanisms	Functional features
V1 domain (ATP hydrolysis, energy supply)			
ATP6V1A	Upregulated in breast, gastric cancers	mTORC1 activation, glycolytic reprogramming	Promotes proliferation and invasion
ATP6V1B1	Upregulated in renal clear cell carcinoma	pH homeostasis, metabolic regulation	Enhances survival
ATP6V1B2	Upregulated in glioma, breast cancer	PI3K/AKT, HIF-1α signaling	Promotes angiogenesis
ATP6V1C1	Upregulated in lung, breast cancer	Wnt/β-catenin, EMT	Drives invasion and metastasis
ATP6V1D	Upregulated in gastric and colorectal cancer	Mitochondrial energy metabolism	Supports energy demands
ATP6V1E1	Upregulated in multiple cancers	mTORC1, acidic microenvironment adaptation	Promotes hypoxia tolerance
ATP6V1F	Upregulated in melanoma	Endocytosis/autophagy regulation	Enhances survival
ATP6V1G1	Upregulated in leukemia, breast cancer	AKT/mTOR signaling	Anti-apoptotic effect
ATP6V1G3	Upregulated in prostate cancer	Hormone receptor signaling	Linked to androgen pathways
ATP6V1H	Upregulated in multiple solid tumors	Autophagy, lysosomal homeostasis	Supports metabolic adaptation

Continued

V0 domain (membrane, proton translocation)			
ATP6V0A1	Upregulated in liver, lung cancers	HIF-1α, hypoxia adaptation	Promotes angiogenesis
ATP6V0A2	Upregulated in colorectal cancer	Glycolytic metabolism	Enhances invasion
ATP6V0C	Upregulated in breast, gastric cancers	Lysosomal acidification	Promotes drug resistance
ATP6V0D1	Upregulated in lung, breast cancers	Autophagy regulation	Promotes survival
ATP6V0D2	Downregulated in clear cell renal cell carcinoma Upregulated in breast, esophagus cancers	Apoptosis, differentiation	Potential tumor suppressor
ATP6V0E1	Upregulated in multiple cancers	mTORC1, Wnt signaling	Promotes proliferation
TCIRG1	Upregulated in osteosarcoma, breast cancer	Lysosomal function	Facilitates invasion and metastasis

6. Oncogenic Mechanisms of ATP6V Family Genes in Tumor Progression

Proton gradients established by V-ATPases play a central role in modulating oncogenic signaling pathways. Lysosomal V-ATPase activity creates a local acidic environment that facilitates the recruitment of the Ragulator-Rag GTPase complex, enabling mTORC1 activation on the lysosomal surface and promoting anabolic metabolism and cell growth [28]. Extracellular acidification driven by V-ATPase enhances Wnt/β-catenin signaling by modulating endosomal trafficking and receptor recycling, stabilizing β-catenin and augmenting its nuclear translocation [29]. In addition, V-ATPase-induced acidosis contributes to HIF-1α stabilization under hypoxic or pseudo-hypoxic conditions by inhibiting prolyl hydroxylase activity, preventing HIF-1α degradation, and promoting angiogenesis and metabolic reprogramming [30]. Collectively, these findings highlight how V-ATPase-mediated pH regulation acts as a central hub coupling cellular metabolism with major oncogenic signaling cascades.

Building on these mechanistic insights, ATP6V gene clusters are deeply involved in shaping malignant phenotypes through multiple molecular mechanisms. Their core regulatory networks center around three key modules: acidification of the tumor microenvironment, lysosomal remodeling, and metabolic reprogramming. Overexpression of V-ATPase proton pump subunits encoded by ATP6V genes induces extracellular acidification, which activates MMPs and EMT pathways, thereby enhancing tumor invasiveness and metastasis. Concurrently, they promote immune evasion by suppressing T- and NK cell-mediated immune surveillance. V-ATPase also maintains lysosomal acidity, supporting autophagy-dependent survival mechanisms and resistance to chemotherapy [31]. Additionally, ATP6V genes activate HIF-1α and mTORC1 signaling, promoting the Warburg effect and cell proliferation [32]. Subunits such as ATP6V0D1 and ATP6V1H aberrantly activate Wnt/β-catenin and EGFR/AKT signaling pathways, contributing to cellular transformation and tumor progression [20] [33].

These complex regulatory networks render ATP6V a promising multi-target strategy for therapeutic intervention.

7. Dual Roles and Controversies in Oncogenic and Tumor-Suppressive Functions of ATP6V Family Genes

The role of ATP6V family genes in cancer remains controversial due to their dual nature—acting as either oncogenes or tumor suppressors depending on the context. Evidence indicates pronounced regulatory heterogeneity of these genes in malignancies [34]. For instance, ATP6V1C1 and ATP6V0A1 promote tumor progression via microenvironmental acidification (pH 6.0 - 6.5), MMP2/9 activation, and sustained autophagic flux. Clinical data from triple-negative breast cancer cohorts associate their overexpression with poor prognosis [35]. Conversely, ATP6V0D2 exhibits tumor-suppressive functions in clear cell renal cell carcinoma, and its deletion accelerates tumor progression [36]. This heterogeneity may arise from subunit-specific functions (e.g., ATP6V1C1 as oncogenic vs. ATP6V0D2 as tumor-suppressive), dynamic regulation during tumor stages, and pH-dependent bidirectional modulation. Single-cell multi-omics approaches are proposed to explore the spatiotemporal expression of subunits, and the development of subunit-specific inhibitors (e.g., NTB1 targeting ATP6V1C1) holds promise for precision therapy. However, the potential for compensatory inflammatory responses following subunit deletion must be considered [10]. These findings underscore the plasticity of the V-ATPase complex in tumor metabolism regulation and emphasize the need for subunit-specific therapeutic targeting. Nonetheless, gene expression and function are often modulated by environmental factors such as chronic inflammation, hormonal changes, and lifestyle, which may influence their oncogenic potential. Thus, interpreting ATP6V's function solely at the genetic level may be overly simplistic.

In different cancer types, ATP6V0D2 (V-ATPase V0 subunit d2) exhibits significant functional heterogeneity, acting as either a tumor suppressor or a promoter of tumor progression. In clear cell renal cell carcinoma (ccRCC), studies indicate that Atractylenolide I (ATL-I) upregulates ATP6V0D2, facilitating autophagic degradation of EPAS1/HIF2*α*, thereby reducing VEGFA production, inhibiting angiogenesis, and reversing sunitinib resistance. Upregulation of ATP6V0D2 also enhances lysosomal function, promotes autophagosome-lysosome fusion, and accelerates HIF2*α* degradation, further suppressing tumor angiogenesis and drug resistance [36]. In contrast, in breast cancer, ATP6V0D2 is highly expressed, particularly in triple-negative breast cancer (TNBC), where its elevated expression correlates with poor prognosis, altered immune microenvironment, and tumor progression [37]. These differences suggest that the function of ATP6V0D2 is highly context-dependent, influenced by cancer type, microenvironmental conditions, and its expression level and activity. Overall, ATP6V0D2 may exert opposite biological roles in different tumor settings, and the precise regulatory mechanisms require further investigation.

8. Therapeutic Prospects and Future Research Directions Targeting the ATP6V Gene Family

V-ATPase inhibitors are considered to have significant antitumor potential due to their ability to regulate tumor microenvironment acidification and inhibit tumor cell survival and metastasis. Classic inhibitors such as Bafilomycin A1, Concanamycin A, and Archazolid act on different V-ATPase subunits to block proton transport or ATP hydrolysis, thereby reducing extracellular acidity, and suppressing tumor cell migration, invasion, and drug resistance [38]-[40]. Next-generation inhibitors (e.g., NiK12192, FR202126) and subunit-specific agents targeting isoforms such as V0a2, including monoclonal antibodies or small molecules, have shown in preclinical studies the ability to slow tumor growth and enhance antitumor immune responses, with relatively low toxicity toward normal cells [41] [42]. Additionally, V-ATPase inhibitors exert antitumor effects through multiple mechanisms, including upregulating TNF-α expression in M1 macrophages, inducing tumor cell apoptosis, and inhibiting mTOR signaling [43]. In models of acute myeloid leukemia, ovarian cancer, breast cancer, and other malignancies, V-ATPase inhibitors have demonstrated dose-dependent antiproliferative and pro-apoptotic effects, although sensitivity varies among patients and tumor types [43]. Overall, V-ATPase inhibitors hold promising prospects as anticancer agents, but their clinical application requires further optimization to improve selectivity and reduce toxicity.

However, broad inhibition of V-ATPase may have limitations and cause systemic toxicity. Studies have shown that V-ATPase inhibition can lead to energy metabolism disorders, mitochondrial damage, increased reactive oxygen species (ROS), and impaired glycolysis, resulting in neurotoxicity and cellular dysfunction [44]. In cancer and healthy cells, V-ATPase inhibition differentially regulates AMP-activated protein kinase (AMPK); in healthy cells, AMPK activation provides a protective effect, whereas in cancer cells this protective mechanism is weakened, rendering tumor cells more susceptible to death [45]. Furthermore, V-ATPase inhibition can disrupt vesicular trafficking, cytoskeletal remodeling, and lysosomal function, potentially causing reduced cell migration, lysosomal acidification defects, and related pathologies (such as lysosomal dysfunction observed in Alzheimer's disease models) [46]. In animal studies, some V-ATPase inhibitors (e.g., bafilomycin) have shown limited systemic toxicity, although the specific adverse effects depend closely on dosage, tissue type, and individual variability [47]. Taken together, non-specific V-ATPase inhibition may indeed lead to gastrointestinal discomfort, electrolyte imbalances, and other systemic adverse effects, which need to be carefully considered in clinical applications.

Taken together, V-ATPase represents a promising yet complex target for cancer therapy. While inhibitors have demonstrated significant preclinical efficacy by modulating tumor acidity, inducing apoptosis, and enhancing antitumor immunity, their clinical translation requires careful consideration of selectivity, subunit specificity, and potential systemic toxicity. Future research should focus on devel-

oping isoform-specific inhibitors, optimizing targeted delivery systems, and elucidating context-dependent mechanisms to maximize therapeutic benefit while minimizing adverse effects. A comprehensive understanding of V-ATPase biology will be essential for translating these strategies into safe and effective anticancer therapies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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