WHIOCE PUBLISHING PTE. LTD.
PROVIDING
FIRST-CLASS SCIENTIFIC INFORMATION
FOR TOP SCHOLARS

2026 Volume 11, Issue 4
Advances in Precision Medicine
ISSN: 2424-9106 (Online)
ISSN: 2424-8592 (Print)

Research Progress on the Function and Application of VCP in Various Cancers

Hao Wang, Tao Wu*
China Pharmaceutical University Jiangsu Key Laboratory of Tumor Occurrence and Intervention, Nanjing 210003, Jiangsu, China

Author to whom correspondence should be addressed.

Abstract: Valosin-containing protein (VCP/p97) is a core member of the AAA + ATPase family and functions as a "ubiquitin-dependent molecular chaperone/segregase, " playing a pivotal role in endoplasmic reticulum-associated degradation (ERAD), protein homeostasis, DNA damage response, organelle quality control (mitochondria/lysosomes), and signaling pathway regulation. Recent basic research has demonstrated that VCP is closely associated with malignant progression in various solid tumors by regulating processes such as tumor cell stress adaptation, proliferation and survival, invasion and metastasis, dryness maintenance, and chemoradiotherapy response, and exhibits "non-pharmacological" applications including prognostic evaluation and molecular subtyping. This article focuses on the expression characteristics, key mechanisms, and application research progress of VCP in five tumor types: esophageal cancer, gastric cancer, colorectal cancer, prostate cancer, and lung cancer, aiming to provide references for further mechanistic elucidation and clinical translation.

Keywords: VCP/p97; Protein homeostasis; ERAD; DNA damage response; Tumor prognosis; Tumor dryness

Online publication: April 26, 2026

1. Introduction

VCP (including vallesterase) is a highly conserved ATPase with high abundance expression in eukaryotic cells, accounting for approximately 1% of cellular soluble proteins[1]. As a "multifunctional" molecular chaperone, VCP possesses two ATPase functional domains that provide energy through ATP hydrolysis, extruding target proteins from macromolecular complexes or cell membranes for proteasomal degradation[2]. Consequently, VCP plays a critical role in protein quality control (particularly the endoplasmic reticulum-associated degradation (ERAD) pathway), preventing abnormal folded protein accumulation and maintaining cellular homeostasis[3]. Beyond protein degradation, VCP is involved in various cellular processes including cell cycle progression, apoptosis regulation, DNA damage response, chromatin remodeling, membrane fusion, and autophagy[4]. The functional diversity of VCP stems from its numerous interacting factors and cofactors. By binding to different auxiliary proteins, VCP mediates the disassembly and degradation of specific substrates, enabling precise spatiotemporal regulation within cells[3, 5]. These properties make VCP a pivotal protein for maintaining cellular homeostasis. Dysfunction or dysregulation of VCP can lead to various pathological states, including neurodegenerative diseases and tumors. Notably, extensive studies have demonstrated that VCP is overexpressed in

multiple human malignancies and often correlates with malignancy severity and prognosis[4, 6]. Elevated VCP levels are believed to confer enhanced survival and growth advantages to cancer cells, making it one of the focal molecules in recent tumor research[7]. The following sections will provide a detailed introduction to the role of VCP in tumorigenesis and development, as well as research progress, categorized by different tumor types.

2. Expression and Mechanistic Role of VCP in Different Cancer Types

Numerous studies have demonstrated that VCP is highly expressed in various human malignant tumors and significantly correlates with tumor invasion and metastasis capabilities as well as patient prognosis[8]. The following sections respectively describe the expression levels, functional roles, and related mechanisms of VCP in major cancer types.

2.1. VCP in Esophageal Cancer

VCP expression in esophageal cancer tissues is significantly higher than in normal tissues and is closely associated with disease progression and metastatic potential [9]. This study suggests that VCP may serve as one of the independent indicators for poor prognosis in esophageal cancer. Mechanistically, although in-depth functional studies on VCP in esophageal cancer are relatively limited, given its pro-NF-κB activity, it is reasonable to hypothesize that overexpression of VCP may promote esophageal cancer cell invasion and anti-apoptosis by activating NF-κB and other pro-survival signaling pathways[10]. Early studies have indicated that VCP is correlated with anti-apoptotic and metastatic capabilities, with its mechanisms involving activation of the nuclear factor κB (NF-κB) signaling pathway. Therefore, in esophageal cancer cells, high VCP expression may enhance NF-κB activation by promoting IκBα degradation, thereby increasing cancer cell resistance to apoptotic stimuli and facilitating infiltration and metastasis[11]. Overall, existing evidence supports the critical role of VCP in esophageal cancer development, with high expression correlating with greater tumor invasiveness and poorer prognosis. This provides a theoretical basis for future exploration of VCP as a potential biomarker or therapeutic target in esophageal cancer.

2.2. VCP in gastric cancer

In gastric cancer, VCP also exhibits abnormally high expression and is significantly associated with tumor malignancy progression. A study by Yamamoto et al. on 330 patients with gastric adenocarcinoma revealed that approximately 70% of patients had tumor tissues with VCP expression intensity higher than normal controls[12]. Patients with high VCP expression tended to have larger tumor volumes, lower differentiation, and higher proportions of vascular and lymphatic invasion, lymph node metastasis, and deeper tumor invasion. Prognostic analysis showed that the tumor-free survival and overall survival of high VCP expression groups were significantly shorter than those of low expression groups ($P < 0.0001$). Multivariate analysis confirmed that high VCP expression is an independent prognostic factor for poor survival in gastric cancer patients. These clinical associations suggest that VCP promotes gastric cancer invasion, metastasis, and progression [9]. Mechanistically, studies have demonstrated that VCP enhances cancer cell survival and metastatic capacity through the NF-κB pathway. It is hypothesized that in gastric cancer, high VCP may promote IκBα protein degradation, continuously activate NF-κB, thereby strengthening cancer cell anti-apoptotic capacity and facilitating lymphatic metastasis[13]. Additionally, VCP-mediated protein degradation may maintain elevated metabolic and protein synthesis loads within gastric cancer cells, enabling them to adapt to hypoxic and nutrient-deficient stress environments. Although further research is needed to elucidate the molecular mechanisms of VCP in gastric cancer, current evidence indicates that VCP is a critical participant in gastric cancer progression, and its expression levels can be used to predict patient prognosis [14].

2.3. VCP in Colorectal Cancer

Colorectal cancer is one of the earliest tumor types found to be closely associated with VCP expression levels. Studies have shown that nearly 70% of colorectal cancer patients exhibit high VCP expression in their primary tumors, while

benign adenoma tissues generally demonstrate low VCP expression, and metastatic lesions almost invariably exhibit high expression. Colorectal cancers with high VCP expression significantly outperform those with low expression in terms of tumor invasion depth (T3-4 vs T1-2), venous invasion incidence, and clinical staging (III-IV vs I-II) (all $P < 0.05$) [12]. More importantly, high VCP expression is significantly associated with increased recurrence rates ($P < 0.001$) and poorer disease-free survival and overall survival rates. Multivariate analysis confirmed that VCP expression level serves as an independent prognostic factor for disease recurrence and survival in colorectal cancer patients[9]. This series of clinical evidence strongly suggests that VCP plays a promoting role in the malignant progression of colorectal cancer. At the fundamental research level, VCP may influence colorectal cancer cell behavior through multiple pathways: on one hand, the UPS function of VCP can modulate cell cycle regulation and homeostasis of apoptosis-related proteins, thereby promoting cancer cell proliferation and survival; on the other hand, VCP may synergize with signaling pathways such as NF-κB to enhance cancer cell invasion and metastatic capacity[8, 15]. For instance, studies have found that the activity of the ubiquitin-proteasome system (UPS) correlates with the metastatic potential of colorectal cancer cells, and as a key enzyme in the UPS, VCP may regulate tumor metastatic potential through the NF-κB signaling pathway.Furthermore, recent studies have reported that VCP participates in regulating the adhesion and scaffold remodeling processes of colorectal cancer cells (e.g., influencing cell motility through the Rho/ROCK pathway) [16]. In summary, high expression of VCP in colorectal cancer not only serves as a marker of disease invasiveness but also promotes cancer cell proliferation and metastasis at the molecular level, making it a potential important molecular target for colorectal cancer [17].

2.4. VCP in Prostate Cancer

In prostate cancer, high expression of VCP is also closely associated with tumor progression and poor prognosis. Studies have reported that patients with prostate cancer exhibiting high VCP expression often have shorter progression-free survival and higher rates of biochemical recurrence [18, 19]. As early as 2004, analyses indicated that VCP overexpression was significantly correlated with poorer survival outcomes in prostate cancer patients. Beyond its prognostic relevance, VCP plays a unique role in the tolerance of prostate cancer cells to androgen deprivation therapy. Androgen-resistant prostate cancer (CRPC) frequently exhibits neuroendocrine differentiation (NED), where tumor cells lose androgen receptor characteristics and instead express neuroendocrine markers, demonstrating enhanced invasiveness and resistance to endocrine therapy [19]. Recent research has identified VCP as a key mediator in the NED process of prostate cancer. Experimental studies have shown that under NED-inducing stimuli (e.g., interleukin-6), VCP expression is significantly upregulated in prostate cancer cell lines LNCaP and VCaP, accompanied by increased levels of neuroendocrine markers such as NSE and plasma membrane chromatin A. In human prostate cancer neuroendocrine-like cell lines (e.g., PC3, NCI-H660), baseline VCP levels are inherently higher than those in adenocarcinoma cell lines. Application of the selective VCP inhibitor NMS-873 significantly suppresses NED-related phenotypes (e.g., reduced expression of neuroendocrine markers), suggesting that VCP activity is essential for maintaining NED. Mechanistic studies further reveal that VCP drives NED by regulating the Pim1 kinase/c-Myc pathway and autophagy processes. Specifically, VCP overexpression increases the expression levels of Pim1 and c-Myc, whereas inhibition of VCP reduces both proteins and is accompanied by a decrease in NED markers [20]. Pim1 is a tumor-survival-promoting kinase that is upregulated under androgen blockade conditions. Experimental studies have demonstrated that inhibition of Pim1 activity or knockdown of c-Myc attenuates VCP-induced NED, indicating that the Pim1/c-Myc pathway plays a central role in this process[21]. The VCP-mediated enhancement of autophagy involves the AMPK pathway, with studies demonstrating that AMPK-activating LKB1 is essential for VCP-induced necrotic endocrine degeneration (NED) and autophagy [22]. In summary, during the transition of prostate cancer cells to a neuroendocrine phenotype under castration stress, VCP confers survival and differentiation potential by upregulating Pim1 and c-Myc and enhancing autophagic clearance. This finding expands our understanding of VCP's function, revealing its role not only in tumor proliferation and apoptosis but also in mediating phenotypic plasticity transformation in cancer cells[23]. Clinically, patients with castration-resistant prostate cancer (CRPC) accompanied by NED often exhibit poor prognosis [24], underscoring the critical research and therapeutic significance of VCP's role in this

process. Future investigations into whether inhibition of VCP or related pathways can block NED occurrence and delay drug resistance progression warrant further exploration.

2.5. VCP in Lung Cancer

VCP was also found to be highly expressed in non-small cell lung cancer (NSCLC) and is closely associated with patient prognosis[4, 25]. A study of surgical tissues from NSCLC patients demonstrated that VCP overexpression was significantly correlated with shorter disease-free survival (DFS) and overall survival (OS), regardless of whether patients were in early or advanced stages. Therefore, VCP can serve as a poor prognostic marker for NSCLC. Valle et al. were the first to elucidate the role of VCP in the pathogenesis and progression of NSCLC. They observed markedly elevated VCP levels in NSCLC tumor tissues and cell lines compared to normal lung tissues. Functional studies revealed that inhibition of VCP (using siRNA/shRNA or small molecule inhibitors) effectively blocked NSCLC cell proliferation, migration, and invasion, and induced apoptosis through G0/G1 phase cell cycle arrest. Mechanistically, VCP inhibition prevents the normal degradation of p53 protein, leading to its accumulation and exerting an anticancer effect, which may explain the controlled tumor cell growth observed after VCP suppression. These findings underscore the critical role of VCP in lung cancer cell survival and malignant behavior[4].

3. Summary and Prospects

For clinical applications, VCP is not only an attractive tumor marker but also a highly promising therapeutic target. The development of multiple VCP small-molecule inhibitors and preliminary trial results have provided feasibility evidence for targeted VCP therapies. From the discovery of lead compounds such as DBeQ to the introduction of candidate drugs like CB-5083 and CB-5339, scientists are progressively overcoming challenges in pharmacokinetics and selectivity, with increasingly superior VCP inhibitors emerging. Concurrently, combining VCP inhibition with conventional therapies (e.g., chemoradiotherapy, targeted drugs) and emerging immunotherapies may yield synergistic effects, enhancing treatment response rates in refractory tumors. Successful outcomes in animal models have laid the foundation for future clinical trials. Looking ahead, with deeper understanding of VCP molecular mechanisms and ongoing inhibitor development, we anticipate witnessing VCP transition from laboratory research to clinical practice. VCP-targeted therapy holds potential to provide novel treatment options for diverse cancer patients, improving efficacy and prognosis. However, challenges such as drug tolerance and safety must be addressed through precision medicine approaches to identify patient subpopulations suitable for VCP-targeted therapy and optimize dosing regimens to reduce toxicity. In summary, as a critical node connecting multiple stages of tumor development, the vigorous progress in VCP functional and applied research will pave new pathways for comprehensive cancer treatment, warranting continued exploration and attention.

Disclosure statement

The author declares no conflict of interest.

References

[1] Pontifex CS, Zaman M, Fanganiello RD, et al., 2024, Valosin-Containing Protein (VCP): A Review of Its Diverse Molecular Functions and Clinical Phenotypes. Int J Mol Sci, 25(11): 5633.

[2] Li C, Huang Y, Fan Q, et al., 2021, p97/VCP is highly expressed in the stem-like cells of breast cancer and controls cancer stemness partly through the unfolded protein response. Cell Death Dis, 12(4): 286.

[3] Carrera Espinoza MJ, Tucker SK, Sureshkumar S, et al., 2025, Harnessing p97/VCP: A Transformative AAA+ ATPase

Target for Next-Generation Cancer Therapeutics. Cancers (Basel), 17(18): 2945.

[4] Valle CW, Min T, Bodas M, et al., 2011, Critical role of VCP/p97 in the pathogenesis and progression of non-small cell lung carcinoma. PLoS One, 6(12): e29073.

[5] Madsen L, Seeger M, Semple CA, et al., 2009, New ATPase regulators--p97 goes to the PUB. Int J Biochem Cell Biol, 41(12): 2380-2388.

[6] Kracht M, Van Den Boom J, Seiler J, et al., 2020, Protein Phosphatase-1 Complex Disassembly by p97 is Initiated through Multivalent Recognition of Catalytic and Regulatory Subunits by the p97 SEP-domain Adapters. J Mol Biol, 432(23): 6061-6074.

[7] Liu Y, Hei Y, Shu Q, et al., 2012, VCP/p97, down-regulated by microRNA-129-5p, could regulate the progression of hepatocellular carcinoma. PLoS One, 7(4): e35800.

[8] Pu Z, Duda DG, Zhu Y, et al., 2022, VCP interaction with HMGB1 promotes hepatocellular carcinoma progression by activating the PI3K/AKT/mTOR pathway. J Transl Med, 20(1): 212.

[9] Yamamoto S, Tomita Y, Hoshida Y, et al., 2003, Expression level of valosin-containing protein is strongly associated with progression and prognosis of gastric carcinoma. J Clin Oncol, 21(13): 2537-2544.

[10] García-Castillo J, Martínez-Cáceres CM, Bernabé-García M, et al., 2025, MicroRNA 196a contributes to the aggressiveness of esophageal adenocarcinoma through the MYC/TERT/NFκB axis. Mol Oncol, 19(11): 3305-3324.

[11] Kim HJ, Kim HJ, Kim SY, et al., 2025, TBK1 is a signaling hub in coordinating stress-adaptive mechanisms in head and neck cancer progression. Autophagy, 21(8): 1744-1766.

[12] Yamamoto S, Tomita Y, Hoshida Y, et al., 2004, Expression of valosin-containing protein in colorectal carcinomas as a predictor for disease recurrence and prognosis. Clin Cancer Res, 10(2): 651-657.

[13] Asai T, Tomita Y, Nakatsuka S, et al., 2002, VCP (p97) regulates NFkappaB signaling pathway, which is important for metastasis of osteosarcoma cell line. Jpn J Cancer Res, 93(3): 296-304.

[14] Parzych K, Saavedra-García P, Valbuena G N, et al., 2019, The coordinated action of VCP/p97 and GCN2 regulates cancer cell metabolism and proteostasis during nutrient limitation. Oncogene, 38(17): 3216-3231.

[15] Huang Y, Wang F, Lin X, et al., 2023, Nuclear VCP drives colorectal cancer progression by promoting fatty acid oxidation. Proc Natl Acad Sci U S A, 120(41): e2221653120.

[16] Khong ZJ, Lai SK, Koh CG, et al., 2020, A novel function of AAA-ATPase p97/VCP in the regulation of cell motility. Oncotarget, 11(1): 74-85.

[17] Fu Q, Jiang Y, Zhang D, et al., 2016, Valosin-containing protein (VCP) promotes the growth, invasion, and metastasis of colorectal cancer through activation of STAT3 signaling. Mol Cell Biochem, 418(1-2): 189-198.

[18] Tsujimoto Y, Tomita Y, Hoshida Y, et al., 2004, Elevated expression of valosin-containing protein (p97) is associated with poor prognosis of prostate cancer. Clin Cancer Res, 10(9): 3007-3012.

[19] Ducharla D, Reddy Kami Reddy K, Dasari C, et al., 2018, Interleukin-6 induced overexpression of valosin-containing protein (VCP)/p97 is associated with androgen-independent prostate cancer (AIPC) progression. J Cell Physiol, 233(10): 7148-7164.

[20] Yu CC, Yang JC, Chang YC, et al., 2013, VCP phosphorylation-dependent interaction partners prevent apoptosis in Helicobacter pylori-infected gastric epithelial cells. PLoS One, 8(1): e55724.

[21] Wang J, Kim J, Roh M, et al., 2010, Pim1 kinase synergizes with c-MYC to induce advanced prostate carcinoma. Oncogene, 29(17): 2477-2487.

[22] Nakkas H, Ocal BG, Kipel S, et al., 2021, Ubiquitin proteasome system and autophagy associated proteins in human testicular tumors. Tissue Cell, 71: 101513.

[23] Papadopoulos C, Kirchner P, Bug M, et al., 2017, VCP/p97 cooperates with YOD1, UBXD1 and PLAA to drive clearance of ruptured lysosomes by autophagy. EMBO J, 36(2): 135-150.

[24] Farinea G, Calabrese M, Carfì F, et al., 2024, Impact of Neuroendocrine Differentiation (NED) on Enzalutamide and Abiraterone Efficacy in Metastatic Castration-Resistant Prostate Cancer (mCRPC): A Retrospective Analysis. Cells,

13(16): 1396.

[25] Wang Y, Zhang J, Li YJ, et al., 2021, MEST promotes lung cancer invasion and metastasis by interacting with VCP to activate NF-κB signaling. J Exp Clin Cancer Res, 40(1): 301.