# Recent advances in the role of atypical cadherin FAT1 in tumorigenesis (Review)

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**Abstract.** The FAT atypical cadherin 1 (FAT1) gene is the ortholog of the *Drosophila* fat gene and encodes the protocadherin FAT1. FAT1 belongs to the cadherin superfamily, a group of full-length membrane proteins that contain cadherin-like repeats. In various types of human cancer, FAT1 is one of the most commonly mutated genes, and is considered to be an emerging cancer biomarker and a potential target for novel therapies. However, the biological functions of FAT1 and the precise downstream signaling pathways that it mediates have remained to be fully elucidated. The present review discussed the current literature on FAT1, focusing on FAT1 mutations and expression levels, and their impact on signaling pathways and mechanisms in various types of cancer, including both solid tumors and hematological malignancies, such as esophageal squamous cell carcinoma, head and neck squamous cell carcinoma, lung squamous cell carcinoma, hepatocellular carcinoma, glioma, breast cancer, acute lymphoblastic leukemia, acute myeloid leukemia, lymphoma and myeloma. The present review aimed to provide further insights and research directions for future studies on FAT1 as an oncogenic factor or tumor suppressor.

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**Contents**



## 1. Introduction

Drosophila Fat was first described in the early 1920s as a lethal mutation (1). In humans, FAT atypical cadherin 1 (FAT1) is located on chromosome 4q34-35 and consists of 27 exons. FAT1 was the first identified member of the FAT family and one of the most frequently studied FAT proteins (2). The FAT1 gene was cloned from a human T-cell leukemia cell line in 1995 (3) and has since been shown to be associated with a number of human diseases, particularly with various tumors. FAT1 is a type I transmembrane protein composed of extracellular, transmembrane and cytoplasmic domains (4). Studies have shown that the intracellular domain of FAT1 is found in both the nucleus and mitochondria (5,6). Under normal physiological conditions, FAT1 acts as a 'brake' on mitochondrial respiration and regulates the proliferation and migration of vascular smooth muscle cells during injury (7-9). In addition, FAT1 serves as a receptor in signaling pathways regulating cell-cell contact and cell polarity (10-13).

Beyond its role in regulating normal cellular activity, FAT1 is one of the most commonly mutated genes in types of human cancer (14-17). Over the past 20 years, studies have shown that FAT1 regulates various signaling pathways (18-20), including the Wnt/β-catenin, Hippo and MAPK/ERK pathways, thereby affecting tumor-cell proliferation, migration, invasion (21-24), stemness and epithelial-mesenchymal transition (EMT) (25,26). Given the large size of FAT1 mRNA and the 49.2 kDa protein it encodes, understanding the function of FAT1 protein is challenging (27). Currently, the understanding of FAT1's biological functions and the precise downstream signaling pathways that it mediates is limited, but increasing interest in its role in cancer suggests that FAT1 is an emerging cancer biomarker and a potential target for new therapies or monitoring (28).

A recent study conducted a comprehensive pan-cancer analysis of FAT1, utilizing data from The Cancer Genome Atlas and Gene Expression Omnibus, to explore its potential oncogenic mechanisms across 33 types of cancer (29). It was found that FAT1 is highly expressed in a large proportion of tumors, significantly associated with prognosis and has a mutation rate of >10% in >10 types of cancers (29), such as lymphoid neoplasm diffuse large B-cell lymphoma, lung adenocarcinoma, lung squamous cell, uterine corpus endometrial, bladder urothelial, and head and neck squamous cell carcinoma (HNSCC). In numerous types of cancer, FAT1 mRNA expression levels are significantly associated with EMT phenotype-related marker genes, as well as with tumor exosomes (29), immune cells (30), methylation (31), hypoxia-related mutations (32) and autophagy marker genes (29). Considering the critical role of FAT1 in tumorigenesis and progression, this review discusses current research on FAT1 in both solid tumors and hematological malignancies. It focuses particularly on tumor types most closely associated with FAT1 in solid tumors, aiming to deepen the understanding of its role in cancer and provide insights for future research directions.

## 2. FAT1 in solid tumors

*FAT1 and esophageal squamous cell carcinoma (ESCC).* In 2020, it was estimated that there would be over 600,000 new cases of ESCC and 544,000 deaths worldwide, with nearly half of these cases occurring in China (33,34). Whole-genome sequencing studies have identified FAT1 as one of the frequently mutated genes in ESCC (35,36). A Chinese study involving 225 patients with ESCC reported a FAT1 mutation frequency of 16% (37), which is consistent with results from another study (36), indicating that FAT1 is one of the most commonly mutated genes in ESCC and may be a key driver of tumorigenesis and progression. Studies have shown that most FAT1 mutations occur in the cadherin domain and FAT1 expression is significantly reduced in ESCC tissues (38,39). *In vitro* studies have demonstrated that knockdown of FAT1 reduces cell adhesion, increases cell elasticity and accelerates cell migration and invasion (39), which suggests that FAT1 may serve a key role in inhibiting cell proliferation, migration and invasion in ESCC, potentially acting as a tumor suppressor gene (40).

Through chromatin immunoprecipitation and luciferase reporter gene assays, it has been demonstrated that FAT1 transcription is regulated by E2F transcription factor 1 (E2F1), which binds to the FAT1 promoter region. Depletion of E2F1 reduces FAT1 transcription activity and mRNA expression levels, indicating that FAT1 is a direct transcriptional target of E2F1 (41). A further study has shown that FAT1 regulates multiple pathways in ESCC, including the MAPK signaling pathway (42). Knockdown of FAT1 in ESCC cells increases mRNA expression levels of MAPK kinase kinase 8 (MAP3K8), MAP2K2, MAP2K6 and L1 cell adhesion molecule and cadherin 5 involved in cell adhesion processes, and decreases mRNA expression levels of the MAPK signaling pathway inactivator dual specificity phosphatase 6, demonstrating the regulatory role of FAT1 in the MAPK signaling pathway and cell adhesion (41). In addition, FAT1 influences EMT in ESCC cells through the MAPK pathway. FAT1 knockdown reduces E-cadherin expression levels, while increasing N-cadherin, vimentin and Snail expression levels, suggesting that FAT1 regulates EMT in ESCC cells via the MAPK/ERK pathway (42-44). A study has also found that FAT1 downregulation enhances stemness and cisplatin resistance in ESCC cells through the Wnt/β-catenin signaling pathway. Therefore, FAT1 and its downstream gene ATP binding cassette subfamily C member 3 may be potential targets to overcome cisplatin resistance in ESCC (45).

In addition to the MAPK and Wnt/β-catenin signaling pathways, studies have found that FAT1 mutations influence ESCC drug resistance and prognosis through the Hippo-Yes1-associated transcriptional regulator (YAP) signaling pathway. A targeted sequencing study of 201 patients with ESCC identified a specific molecular subtype called FAT/FRY, characterized by mutations in FAT1, FAT3 and FRY microtubule binding protein (FRY). The FAT/FRY subtype showed poor prognosis in multiple ESCC cohorts, characterized by Hippo pathway inactivation, hypoxia, chemotherapy resistance and high infiltration of CD8+ T cells and activated dendritic cells (46). Furthermore, a drug response analysis from the Genomics of Drug Sensitivity in Cancer database conveyed that ESCC cell lines with FAT/FRY mutations were more sensitive to the PIK3Ca inhibitor alpelisib. Alpelisib mitigates tumor growth by inhibiting the phosphorylation of PI3K downstream targets such as AKT and the interaction between the PI3K/AKT pathway and other pathways, such as the Hippo pathway, may affect drug efficacy, warranting further research to determine whether FAT/FRY-type ESCC is more sensitive to alpelisib (46). Another study found that downregulation of FAT1 and protein tyrosine phosphatase non-receptor type 14 (PTPN14) was associated with upregulation of YAP1 in ESCC tissues, indicating that FAT1 may suppress ESCC progression and chemotherapy resistance through upregulation of PTPN14 and inhibition of YAP1 and MYC, thus involving the Hippo-YAP signaling pathway in the malignant progression and chemotherapy resistance of ESCC (47) (Fig. 1).

*FAT1 and HNSCC.* HNSCC is a severe and often fatal disease that affects the upper respiratory and digestive functions of patients, accounting for ~4.6% of cancer-associated deaths worldwide (48). As the sixth most common cancer globally, HNSCC has the highest FAT1 gene mutation rate among various solid tumors. However, the role of FAT1 gene mutations in the pathogenesis and progression of HNSCC and the mechanisms of associated signaling pathway activation remain limited (49-54). The mutation rate of the FAT1 gene in patients with oral squamous cell carcinoma (OSCC), a subtype of HNSCC, is ~17% (55). A study conducted in Korea detected genetic alterations in 44 cases of advanced oral tongue squamous cell carcinoma, with a FAT1 mutation rate of 9.1% (56). In addition, a study conducted in Taiwan performed whole-exome sequencing on 120 samples of OSCC tumors and corresponding normal tissues and identified inactivating FAT1 mutations in 35% of tumors (57). These findings suggest that FAT1 gene mutations may serve a carcinogenic or driver role in OSCC and other HNSCCs (58-61). The differences in reported FAT1 gene mutation rates among different studies may be due to tumor heterogeneity or variations in patient

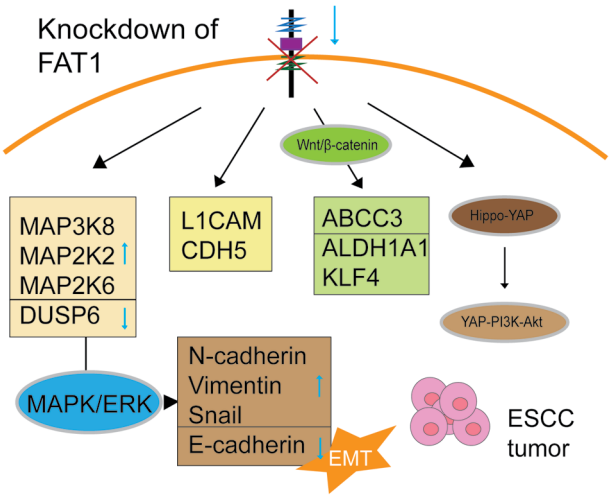


Figure 1. Carcinogenic signaling pathways downstream of decreased FAT1 expression in ESCC tumors, including the MAPK/ERK, Wnt and Hippo-YAP pathways. FAT1, FAT atypical cadherin 1; ESCC, esophageal squamous cell carcinoma; EMT, epithelial-mesenchymal transition; YAP, yes1-associated transcriptional regulator; DUPS6, dual specificity phosphatase 6; CDH5, cadherin 5; L1CAM, L1 cell adhesion molecule; ABCC3, ATP-binding cassette subfamily C member 3; KLF4, Krüppel-like factor 4; ALDH1A1, aldehyde dehydrogenase 1 family member A1.

cohorts. Furthermore, studies indicate differences in tumor biology and genomics between different ethnic populations. For instance, Chaudhary *et al* (62) identified increased mutation frequencies in key driver genes such as FAT1 and TP53 in African American patients with HNSCC compared with human papillomavirus (HPV)-positive or negative white patients. The higher FAT1 mutation frequency in African American patients was significantly associated with decreased survival rates, partially explaining the worse prognosis of HNSCC in this population compared with white patients.

Studies have found that ~50% of patients with HNSCC have somatic alterations in the Hippo-YAP pathway (63,64). In particular, FAT1 gene mutations contribute to the activation of YAP1 transcription, with the FAT1/YAP1 signaling axis directly involved in the development of HNSCC. Proteogenomic and drug screening studies across various types of cancer models have shown that FAT1 mutations sensitize HNSCC cells to JQ1, a bromodomain and extra-terminal domain (BET) family (BRD2, BRD3 and BRD4) inhibitor. In contrast to other types of cancer with Hippo pathway variations, such as ESCC and lung squamous cell carcinoma, FAT1 mutations in HNSCC confer high specificity and sensitivity to BET inhibitors. Further studies have demonstrated that FAT1 knockdown increases cell sensitivity to JQ1 and lowers the $IC_{50}$. Epigenomic analyses demonstrated that FAT1 mutations in HNSCC lead to increased YAP1 nuclear translocation and activation of multiple cancer-related genes such as neuregulin 1 (NRG1), follistatin, ATPase family AAA domain containing 2 and programmed cell death ligand 1 (PD-L1). Persistent activation of NRG1 mediates receptor tyrosine kinase pathway activation, promoting tumor development and drug resistance. Therefore, combining BET inhibitors, erythroblastic leukemia viral oncogene (ErbB) inhibitors or immune checkpoint inhibitors (ICIs) may offer potential therapeutic opportunities for patients with HNSCC with FAT1 mutations (65).

FAT1 mutations in head and neck cancer are closely associated with tumor progression and survival. Knockout of endogenous FAT1 expression and exogenous expression of key domains of FAT1 demonstrate that FAT1 can inhibit the migration and invasion abilities of HNSCC cells (66). Further functional analysis suggests that nonsense mutations in FAT1 result in the loss of its tumor suppressive function, while FAT1 mutations and low expression levels are significantly associated with lymph node involvement, lymphovascular invasion and tumor recurrence (67). Treatment of the HNSCC cell line HO-1-u-1 with PTC124 (also known as Ataluren), a drug used for treating genetic diseases mediated by nonsense mutations, demonstrated that PTC124 could re-express functional FAT1 and thereby rescue FAT1 function in HNSCC cells with nonsense mutations and inhibit cell proliferation (68). Another study used two small interfering RNAs (siRNAs) to reduce FAT1 expression levels in OSCC cell lines *in vitro* to demonstrate that FAT1 silencing inhibited OSCC cell proliferation, stemness, cell cycle and migration, while promoting early and late apoptosis (69). The discrepancy between these findings and aforementioned reports may be due to the different biological functions of FAT1 mutations in contrast to FAT1 expression. Bioinformatics and clinical analyses indicate that although the four most common FAT1 mutation sites were detected in various types of cancer, these variants were not significantly associated with FAT1 expression levels. Thus, the correlation between FAT1 mutations and lower FAT1 expression in tumors remains controversial.

A recent study by Kim *et al* (70) utilized data from four publicly available HNSCC cohorts and a cohort from a tertiary medical center registry to investigate the clinical significance of FAT1 gene mutations and mRNA expression levels in patients with HNSCC. FAT1 expression was significantly increased in HNSCC cell lines with acquired radioresistance, suggesting that FAT1 features could serve as clear indicators to distinguish between radioresistant and non-radioresistant patients with HNSCC. In addition, FAT1 also influences HNSCC sensitivity to chemotherapeutic drugs. Xu *et al* found that FAT1 overexpression was associated with cisplatin resistance, but FAT1 suppression using short hairpin (sh)FAT1 re-sensitized cisplatin-resistant cells to cisplatin, while enhancing glutathione (GSH)/GSH synthetase-mediated oxidative stress and disrupting low-density lipoprotein 5/Wnt2 signaling; this demonstrates a novel role of FAT1 in OSCC tumorigenesis and cisplatin resistance (71). It was also reported that FAT1 can lead to resistance to EGFR-targeted therapy by affecting the EGFR/ErbB signaling pathway, particularly in HPV-negative HNSCC, and may contribute to resistance to EGFR-targeted therapy (Fig. 2) (72).

*FAT1 and non-small cell lung cancer (NSCLC).* Lung cancer is the leading cause of cancer-related death in both men and women worldwide. It is primarily classified into two types: SCLC, which accounts for ~15% of lung cancer cases and NSCLC, which accounts for ~85% of cases. NSCLC is further divided into lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) as the main subtypes. Despite significant therapeutic advances over the past few decades, the recurrence and metastasis rates of NSCLC

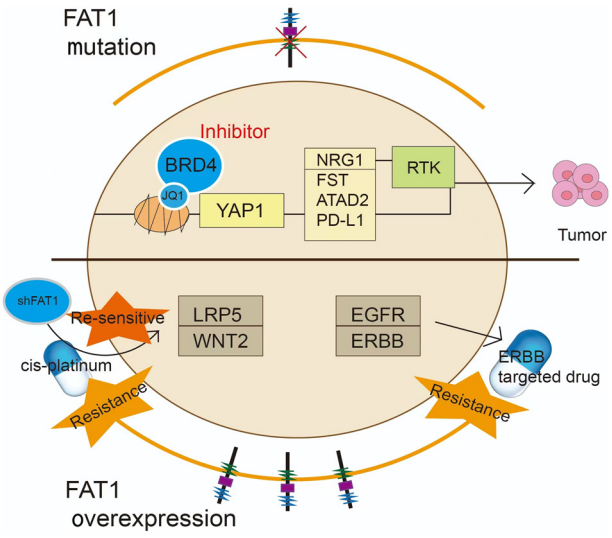


Figure 2. Signaling pathways downstream of FAT1 mutations and overexpression include BRD4 inhibition and resistance towards cisplatin in head and neck squamous cell carcinoma. FAT1, FAT atypical cadherin 1; BRD4, bromodomain-containing protein 4; shFAT1, short hairpin FAT1.

remain high at 30-40%, with a 5-year overall survival rate of <15%. Therefore, there is a pressing need to explore the genetic mechanisms underlying NSCLC, identify prognostic biomarkers and discover new therapeutic targets. Research on FAT1 in lung cancer has primarily focused on NSCLC. A recent study utilized next-generation sequencing (NGS) technology to identify high-frequency mutant genes in 110 Chinese patients with NSCLC. The results showed a FAT1 mutation rate of 12.90%, one of the frequently mutated genes of those analyzed (73). Another study used paired tumor and adjacent lung tissue samples from 112 surgically resected patients with initial treatment for comprehensive proteogenomic characterization of SCLC, further demonstrating the role of FAT1 mutations in carcinogenesis with same findings as above (74). Recent findings suggest that FAT1 deletion in LUSC may lead to an enhanced EMT state, tumor stemness and metastatic ability (25), providing further insight into the potential role and therapeutic targets of FAT1 in lung cancer.

Over the past decade, the identification of key mutations and the introduction of immune checkpoint blockade drugs have revolutionized the therapeutic landscape of NSCLC. Biomarkers such as tumor mutation burden (TMB), T-cell infiltration and PD-L1 protein expression levels in tumor tissues have been proposed as indicators of immune therapy response (75). Studies have indicated that co-mutations of low-density lipoprotein receptor-related protein 1B and FAT1 may serve as a set of potential predictive factors to guide immunotherapy in NSCLC (76). It was reported that patients with FAT1-mutated NSCLC may have higher sustained clinical benefits and objective response rates than FAT1-nonmutated (77). These results were validated in other independent datasets, suggesting that FAT1 mutations could be a robust biomarker for predicting immunotherapy efficacy (77). A Chinese study also reported that patients with NSCLC with FAT1 mutations might be associated with improved ICI treatment outcomes. Genomic and immunological analyses showed that patients with NSCLC with FAT1 mutations often had a high TMB, increased immune-responsive cell infiltration, decreased immune-suppressive cell infiltration and enrichment of IFN and cell cycle-associated pathways. FAT1 mutations are associated with improved immunogenicity and ICIs efficacy, making it a potential biomarker for the selection of patients for immunotherapy (78). A study proposed a model using lung cancer patient genetic mutation profiles, including FAT1 mutations, to predict the survival of patients with various types of cancer using immunotherapy. This predictive model effectively identifies patients with various types of cancer who can benefit from ICIs treatment, potentially providing notable assistance in clinical oncology treatment (79).

*FAT1 and hepatocellular carcinoma (HCC).* HCC is a common type of cancer and the third leading cause of cancer-related death worldwide. HCC poses significant treatment challenges with a 10-20% 5-year overall survival rate, necessitating further research to elucidate the molecular mechanisms of HCC progression and identify new therapeutic targets (32,80). Zhu *et al* (81) found that the POU class 2 homeobox 1 (POU2F1) transcription factor is significantly upregulated in HCC tumor tissues and cell lines compared with healthy tissues, promoting HCC cell growth and metastasis, with FAT1 acting downstream of POU2F1. It was demonstrated that FAT1 is strongly positively expressed in HCC and weakly expressed in the normal liver, with FAT1 upregulation positively associated with lower overall survival rates. *In vitro* experiments demonstrated that transfection of targeted FAT1 shRNA into HepG2 and SNU-423 cells significantly reduced their migration and invasion. In addition, reducing FAT1 levels could reverse POU2F1 overexpression-mediated HCC cell proliferation, colony formation, migration and invasion, suggesting that FAT1 independently regulates HCC metastasis and is a potential new therapeutic target for HCC. Further research indicated that FAT1 is highly expressed in liver cancer tissues and human liver cancer cell lines, whereas miR-223-3p is lowly expressed. Dual-luciferase assay results showed that miR-223-3p inhibits HCC proliferation, migration, invasion and EMT by targeting and downregulating FAT1 expression (82,83).

Glypican-3 (GPC3) is a cell surface heparan sulfate proteoglycan that interacts with several extracellular signaling molecules, including Wnt, hepatocyte growth factor (HGF) and Hedgehog, making it an emerging therapeutic target for HCC (84). A study indicated that FAT1, as a novel GPC3-interacting protein, binds to the C-terminal region of GPC3 (Q14517, residues 3,662-4,181), which contains a putative receptor tyrosine phosphatase-like domain, a laminin G-like domain and five EGF-like domains. GPC3 and FAT1 were found to have similar expression patterns in HCC cells, including enhanced expression and upregulation under hypoxic conditions, and can regulate EMT-related genes such as Snail, vimentin and E-cadherin, promoting HCC cell migration. This research provides preliminary evidence for a novel mechanism by which GPC3 and FAT1 can promote HCC cell migration (85). Overall, FAT1 expression levels are closely associated with HCC occurrence and development. Further exploration of FAT1 mechanisms and its associations with factors such as hypoxia, HGF and methyl donor S-adenosyl-L-methionine is crucial for HCC diagnosis, treatment and prognosis.

*FAT1 and gliomas*. Glioblastoma (GBM) invasiveness is influenced by a hypoxic microenvironment through hypoxia-inducible factor (HIF)1α, while the tumor microenvironment is significantly affected by FAT1 (86,87). A study under severe hypoxic conditions explored the interaction between FAT1 and HIF1α in primary tumors. Findings in GBM tumor specimens indicated a positive association between FAT1 and HIF1α and its target genes, highlighting the importance of the FAT1-HIF1α signaling axis in glioma cells (88). Specific FAT1 siRNA-transfected GBM cell lines were cultured under hypoxia and it was found that reducing endogenous FAT1 expression significantly decreased HIF1α and its downstream target gene expression levels, which also notably reduced the invasiveness of GBM cells. This reduction is attributed to impaired EGFR-AKT signaling and increased von Hippel-Lindau-dependent proteasomal degradation of HIF1α, further suggesting that FAT1 could be a novel potential target for GBM treatment (89). A study also found that FAT1, along with EMT markers (such as Snail, lysyl oxidase, vimentin and N-cadherin), stemness markers (such as sex-determining region y-box 2, POU class 5 homeobox 1, nestin and RE1-silencing transcription factor) and hypoxia markers (such as HIF1α, VEGF, phosphoglycerate kinase 1 and carbonic anhydrase IX) are upregulated in at least 39% of GBM cases. The glioma cell lines U87MG and A172 that were exposed to severe hypoxia (0.2% $O_2$) showed increased mRNA expression levels of FAT1, EMT, stemness and hypoxia markers compared with cells cultured under normoxia (20% $O_2$). Furthermore, FAT1 knockdown in U87MG and A172 cells cultured under both severe hypoxia and normoxia conditions significantly reduced the expression of EMT and stemness markers, suggesting that FAT1 may regulate these markers through independent action from HIF1α, thus suggesting a novel mechanism by which FAT1 regulates EMT/stemness in hypoxic GBM (90).

In GBM, high expression of FAT1 affects the expression of inflammatory factors. Research using high FAT1-expressing grade IV glioma cell lines, such as U87MG and A172, showed that reducing FAT1 expression levels using an siRNA decreased cell migration and invasion capabilities, and also increased the expression levels of the tumor suppressor gene programmed cell death 4 (PDCD4). Increased PDCD4 expression levels suppress the phosphorylation of c-Jun, thereby weakening activator protein (AP)-1 transcriptional activity, which leads to decreased expression levels of AP-1 target genes such as MMP3, VEGF-C and plasminogen activator, urokinase, inflammatory factor cyclooxygenase-2 and cytokines IL-1β and IL-6. This demonstrated a novel FAT1-mediated signaling mechanism that acts as an upstream regulator of oncogenic and inflammatory pathways in GBM by modulating PDCD4 activity (91). A recent study has found that FAT1 is involved in regulating the expression of anti-inflammatory mediators TGF-β1/2 in resected human gliomas, primary glioma cultures and other cancer cell lines, with FAT1 expression correlating positively with TGF-β1/2 level in various tumors. FAT1 knockdown using an siRNA led to reduced expression and secretion of TGF-β1/2, increasing the chemotacticity of THP-1 monocytes to the supernatants of tumor cells transfected with siFAT1, which resulted in immune suppression. Additionally, FAT1 expression was positively correlated with the expression of myeloid-derived suppressor cell (MDSC) markers in gliomas, suggesting that FAT1 may serve a role in MDSC-mediated immunosuppression. Therefore, FAT1 expression levels in various types of cancer are inversely associated with the infiltration of tumor-suppressing immune cells (such as monocytes and T cells) and positively correlated with tumor-promoting immune cells (such as MDSCs). FAT1 serves a significant role in cancer immune evasion, particularly through promoting an immunosuppressive microenvironment in GBM and other types of cancer via TGF-β1/2 (Fig. 3) (92).

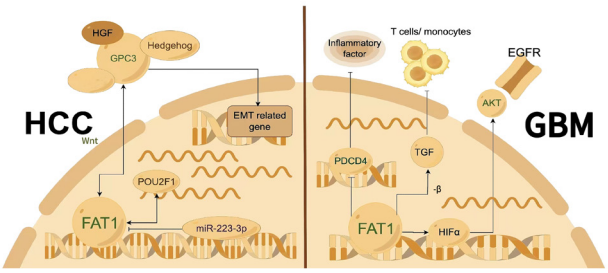


Figure 3. Signaling pathways of FAT1 mutations in HCC and GBM, including POU2F1, GPC3, HIF1α and PDCD4. FAT1, FAT atypical cadherin 1; HCC, hepatocellular carcinoma; GBM, glioblastoma; POU2F1, POU class 2 homeobox 1; GPC3, glypican 3; HIF1α, hypoxia-inducible factor 1 alpha subunit; PDCD4, programmed cell death 4.

*FAT1 and breast cancer*. Significant progress has been made in understanding the role of FAT1 in breast cancer resistance (93,94). Studies indicated that cyclin-dependent kinase (CDK4/6) inhibitors are somewhat effective against breast cancer, but resistance is notably high. Genomic analysis of 348 patients with estrogen receptor-positive (ER+)/HER2- breast cancer showed that the absence of FAT1 leads to notable resistance to CDK4/6 inhibitors. It was found that loss of FAT1 significantly increases CDK6 expression levels, while inhibition of CDK6 could restore sensitivity to CDK4/6 inhibitors. Further research indicated that the induction of CDK6 is mediated by the Hippo pathway, with the accumulation of YAP and TAZ transcription factors on the CDK6 promoter enhancing resistance to CDK4/6 inhibitors. These findings highlight the anticancer role of the Hippo signaling pathway in ER+ breast cancer and identify the absence of FAT1 as a mechanism leading to resistance to CDK4/6 inhibitors (95,96) (Fig. 4).

Aldehyde dehydrogenase 1 (ALDH1) is considered a marker of breast cancer stem cells and its enzymatic activity is crucial for the regulation of cancer stem cells. A recent study found that KK-LC-1 (also known as CT83 or Cxorf61), a type of testicular cancer antigen, can interact directly with FAT1, leading to its ubiquitin-mediated proteasomal degradation. This process regulates the expression levels of FAT1, which in turn influences the stemness of ALDH+ cells in triple-negative breast cancer (TNBC). Degradation of FAT1 affected the Hippo pathway and led to YAP1 nuclear translocation and ALDH1A1 transcription. These findings identified the KK-LC-1-FAT1-Hippo-ALDH1A1 pathway as a potential therapeutic target in TNBC, providing a novel research direction for the treatment of breast cancer (97).

*FAT1 in other common types of cancer*. A study indicated that, in addition to the role in breast cancer, FAT1 is involved

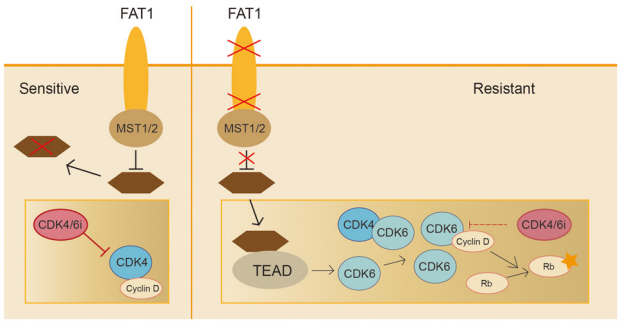


Figure 4. Loss of FAT1 promotes resistance to CDK4/6 inhibitors through the Hippo pathway in breast cancer; genes in a yellow box are nuclear signaling. FAT1, FAT atypical cadherin 1; MST1/2, macrophage stimulating 1/2; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; Rb, retinoblastoma protein; TEAD, transcriptional enhanced associate domain.

in the development and progression of various other malignancies, including bladder, prostate, uterine, colorectal and gastric cancer (GC) (98,99). Early genome-wide sequencing identified recurrent protein-inactivating mutations in FAT1 among 14 different grades and stages of bladder cancer (100). An *in vitro* study reported that S100 calcium binding protein A14 (S100A14) promotes the expression of FAT1 and activates the Hippo pathway, thereby inhibiting the growth and EMT of prostate cancer. *In vivo* results confirmed that S100A14, mediated through the FAT1-driven Hippo pathway, inhibits tumor growth in mouse prostate cancer cells (101). Evidence also closely associates FAT1 with the progression of GC (102). A study showed that FAT1 is upregulated in GC tissues and silencing FAT1 inhibits the oncogenic phenotype of GC cells. A further mechanistic study indicated that LINC00857 serves an oncogenic role in GC by regulating the transcription factor AP-2 gamma/FAT1/AP-1 pathway (103).

Colorectal cancer (CRC) consists of tumors of the colon, rectum and anus and represents the third most common cancer type, accounting for 10% of new cancer cases globally with 935,173 deaths in 2020. Studies suggest that FAT1 is a key gene promoting cancer cell migration and growth, and, compared with normal colon tissues, is highly expressed on the plasma membrane of colon cancer cells (104-106). The discovery of novel molecules that can inhibit the expression of FAT1 and its downstream signaling pathways is crucial for the development of new anti-CRC drugs. Dehydroabietic acid (DIAP) is a specific natural product mainly found in the *Hypericum perforatum* Linn. HPLC-UV screening identified 46 DIAPs in *H. perforatum* Linn roots, with compounds 2 and 6 showing potent and selective cytotoxicity against colon cancer cells, significantly inhibiting NF-κB and FAT1 expression in HCT116 cells and promoting the novel tumor suppressor gene PDCD4. These effects are mediated through the FAT1 signaling pathway. Therefore, DIAPs may be further studied as a new type of anti-CRC lead drug targeting FAT1 (107).

NGS analysis of 111 patients diagnosed with CRC highlighted the complex heterogeneity of genetic alterations within CRC (108). Currently, immunotherapy is approved for CRC tumors with high microsatellite instability. Targeted sequencing using the tumor tissues of 161 patients with CRC demonstrated that, compared with the wild-type FAT1 gene, FAT1 gene mutation of CRC with microsatellite instability events often occur simultaneously and showed a higher TMB. Kyoto Encyclopedia of Genes and Genomes pathway analysis showed that the PI3K-AKT pathway and immune pathways were altered in CRC tissue samples with mutant FAT1. Tumor samples with FAT1 mutations from patients with CRC showed improved characteristics for immunotherapy. Although the studies were conducted retrospectively and further *in vitro* experiments are necessary to verify the association between FAT1 mutations and the immune environment of CRC tumors, this suggested that tumors with FAT1 mutations may define a new subtype of CRC immunocompetence (30,109). Therefore, in future immunotherapy trials, FAT1 gene mutations in patients with CRC may be considered a specific subgroup for further study.

## 3. FAT1 in hematological malignancies

*FAT1 and acute lymphoblastic leukemia (ALL).* FAT1 was initially cloned from a human T-cell ALL cell line, indicating its expression in ALL (110,111). Feng *et al* (112) used targeted NGS to analyze 112 genes from 121 adult patients with ALL. In the group studied, 110 patients (90.9%) carried at least one mutation, including the five most common mutated genes, with FAT1 at the top. In B-cell ALL (B-ALL), FAT1 mutations are among the most common (10.75%), suggesting that gene mutations are prevalent in adult patients with ALL, with FAT1 mutations potentially being a pathogenic factor. Another study involving 147 adolescent and adult patients with ALL analyzed by NGS showed that 91.2% of the patients carried at least one mutation, with 67.35% carrying multiple (≥2) mutations. FAT1 mutations are more common in B-ALL compared with T-ALL (113). In addition, a study on genetic variations in pediatric T-ALL identified 302 mutations across 60 genes, with FAT1 (32.81%) showing a higher mutation frequency, suggesting that FAT1 mutations are more common in pediatric patients with ALL (114). These results indicate that FAT1 mutations are common genetic alterations in both children and adults with ALL, potentially driving the disease's progression and possibly affecting prognosis.

In addition to the presence of FAT1 mutations, the expression of FAT1 also serves a significant role in ALL. de Bock *et al* (115) found that FAT1 protein is expressed in various leukemia cell lines, but not in healthy peripheral blood and bone marrow cells. Further clinical leukemia data analysis showed that in 11% of AML, 29% of B-cell ALL (B-ALL) and 63% of T-cell ALL (T-ALL), FAT1 transcription levels rise significantly, and normal peripheral blood or bone marrow cells show little or no FAT1 transcription. Furthermore, in two independent studies using matching diagnosis-relapse samples from children with precursor B-cell (pre-B)-ALL, high FAT1-mRNA expression at diagnosis predicted shorter relapse-free and overall survival. Data suggest that the expression of FAT1 in pre-B-ALL is associated with the occurrence of relapse and can provide a suitable therapeutic target for high-risk pre-B-ALL. Another study on adult acute leukemia analyzed the expression levels of FAT1 in samples from healthy donors, patients with AML, adult T-ALL and pre-B-ALL, and various leukemia cell lines (116). In bone marrow from healthy donors, CD34+ progenitor cells, peripheral blood and CD3+ T cells were found not to express FAT1, whereas FAT1

was highly expressed in bone marrow mesenchymal stromal cells from healthy donors. By contrast, adult leukemic samples showed abnormal FAT1 expression and FAT1 expression was associated with a more mature leukemia immune phenotype. Further investigation demonstrated that FAT1 mutations were present in early T-ALL (25%) and thymic T-ALL (12%), but not in T-ALL with a mature immunophenotype. No differences in overall survival rates or duration of response were observed between patients with mutant and normal FAT1. Although FAT1 was not of significant prognostic value, FAT1 may be considered a potential candidate for disease monitoring, targeted therapy and insight into the pathogenesis of leukemia in different ALL subgroups. In addition to the potential role of leukemia, FAT1 is also involved in cell migration, polarity and intercellular adhesion and interact with β-serial protein directly. High FAT1 expression levels were identified in bone marrow mesenchymal stromal cells, suggesting that FAT1 may serve a role in stabilizing the interaction of leukemic cells with bone marrow niches and thymic homing.

Using gene set enrichment analysis, Liu *et al* (117) showed that gene enrichment of the Wnt signaling pathway was found in patients with T-ALL FAT1-positive subgroups, prompt FAT1 may participate in regulating Wnt pathways. Through the generation of FAT1 overexpression, knockdown and knockout cell lines *in vitro*, it was demonstrated that knockdown of FAT1 resulted in impaired cell proliferation and downregulation of Wnt pathway target genes (such as cyclin D1, Myc proto-oncogene protein and lymphoid enhancer-binding factor 1), while overexpression of FAT1 promoted cell proliferation. Abnormal FAT1 expression levels were shown to affect cell proliferation and Wnt signaling pathway regulation. Recently, Liebig *et al* (118) investigated the expression and biological function of FAT1 in T-ALL. It was reported that FAT1 expression was associated with a more mature immunophenotype in leukemia and an inverse relationship between FAT1 expression and its promoter methylation was demonstrated. FAT1 overexpression established in the study employed transfection of truncated but functional FAT1 plasmids. In addition, de Bock *et al* (119) found that T-ALL cell lines and clinical samples with T-ALL in a unique N-terminal truncated FAT1 mRNA transcript. This FAT1 transcript originates from the novel transcription start site and is located in the intronic sequence, producing a truncated protein lacking the entire extracellular domain of FAT1. The truncated form of FAT1 is expressed in T-ALL and serves a role in cell proliferation and colony formation. A study has found that the truncated FAT1 protein may act as an oncogene in the development of T-ALL and interact with NOTCH1 mutation to promote the occurrence of T-ALL *in vivo*. This highlights the function of the full-length FAT1 as these structures may have important negative effects on the signaling of full-length FAT1 or have independent protein signaling functions. Therefore, the aforementioned study provides a key reference for further study on the mechanism of action of full-length FAT1 and its role in T-ALL.

*FAT1 and acute myeloid leukemia (AML).* Garg *et al* (120) conducted targeted sequencing of 299 genes in patients with AML carrying the FMS-like tyrosine kinase-3 internal tandem duplication (FLT3-ITD) mutation and reported a mutation rate of up to 10% in the FAT1 gene. FAT1 is closely related to the onset and development of AML with FLT3-ITD mutations. A clinical study has shown that FAT1 mutations may affect the outcomes of patients with AML after receiving allogeneic hematopoietic stem cell transplantation (HCT) (121). A retrospective clinical study found that among patients with normal karyotype AML receiving allogeneic HCT, the mutation rate for FAT1 was 7.0%, while DNA (cytosine-5)-methyltransferase 3A (DNMT3A) mutations occurred at a rate of 31.3%, with the most common site being R882. Multifactorial analysis indicated that mutations in DNMT3A R882, particularly when with FLT3-ITD mutation, increased the risk of relapse and were significant prognostic factors for poor transplant survival outcomes. Since DNMT3A R882 mutations correlate positively with FAT1 mutations, FAT1 mutations may be associated with adverse outcomes and relapses after allogeneic HCT in AML, potentially acting as a pathogenic driver in AML (122). Clinical research conducted in China by Zeng *et al* (123) also demonstrated that FAT1 mutations are associated with poor prognosis in patients with normal karyotype myelodysplastic syndrome, suggesting that allo-HSCT may not overcome its adverse effects.

A recent study reported that FAT1 suppresses autophagy and proliferation levels in AML by downregulating autophagy-related 4B (ATG4B) expression. The mutation rate of all mutated genes in 22 patients with AML were analyzed and a high FAT1 mutation rate of 40.90% was found, which is notably higher (124). Further analysis using the Gene Expression Profiling Interactive Analysis database indicated that FAT1 mRNA expression levels in AML were significantly lower compared with the control group. These results suggest that FAT1 may serve an anti-tumor role in AML. A study using the AML cell lines KG-1a and THP-1 demonstrated that FAT1 suppresses autophagy in AML by inhibiting TGF-β-SMAD2/3 signal activity, thereby reducing the expression of ATG4B and consequently inhibiting AML proliferation. These findings suggest that the FAT1-TGF-β-SMAD2/3-ATG4B-autophagy pathway may represent a novel target for the development of therapeutic drugs for AML (125).

*FAT1 in lymphoma/myeloma.* Although the FAT1 gene is described as a tumor suppressor in various types of cancer, FAT1 mutations are infrequently found in lymphoma entities. Peripheral T-cell lymphoma (PTCL), not otherwise specified, is the most common subtype among nodal peripheral T-cell lymphomas and is a tumor with strong clinical, histological and molecular heterogeneity. However, its genetic landscape has remained to be fully clarified. A study has shown that a subset of patients with PTCL-NOS exhibit recurrent mutations in the FAT1 gene, which is significant for understanding the pathogenesis of this type of lymphoma. A large proportion of mutations in the FAT1 gene are missense mutations rather than frameshift insertions/deletions or nonsense mutations. Further analysis indicated that tumors in patients with FAT1 mutations are associated with characteristics related to growth, apoptosis, cell migration and invasion. Patients with FAT1 mutations have a shorter overall survival compared with those with wild-type FAT1 (126,127). Furthermore, FAT1 mutations have also been found to be associated with poor prognosis in angioimmunoblastic T-cell lymphoma (AITL). A study involving detailed genetic analysis of blood samples from

Table I. Functions of FAT1 mutation and its expression in various types of cancer and related signaling pathways.

A, Solid tumors

| Type of cancer | FAT1 mutation function | Normal FAT1 expression function | Related signaling pathway |
|---|---|---|---|
| ESCC | + | - | FAT1 knockdown upregulates the MAPK, Wnt/β-catenin and Hippo-YAP signaling pathways. |
| HNSCC | + | + | FAT1 mutation activates the YAP1 signal transduction axis and NRG1 mediates the RTK pathway. |
| NSCLC | + | - | FAT1 mutation upregulates IFN and cell cycle related pathway enrichment. |
| HCC | NA | + | FAT1 is a GPC3 interacting protein that interacts with Wnt, HGF and Hedgehog signaling molecules. |
| GBM | NA | + | FAT1 reduction reduces the expression of HIF1α and its downstream target genes, impairs EGFR-AKT signaling, increases PDCD4 expression and decreases TGF-β1/2 expression/secretion. |
| BC | NA | - | FAT1 deletion leads to a significant increase in CDK6 and resistance to CDK4/6 inhibitors mediated by the Hippo pathway, leading to nuclear translocation of YAP1 and transcription of ALDH1A1. |
| GC | NA | + | FAT1 regulates the TFAP2C/FAT1/AP-1 axis. |
| CRC | NA | + | NA |

B, Hematological malignancies

| Type of cancer | FAT1 mutation function | Normal FAT1 expression function | Related signaling pathway |
|---|---|---|---|
| ALL | + | + | FAT1 activates Wnt signaling target genes (CCND1, MYC and LEF1). |
| AML | + | - | FAT1 downregulates autophagy-associated ATG4B by inhibiting TGF-β-SMAD2/3 signaling activity. |
| Lymphoma | + | NA | NA |

+, oncogene; -, tumor suppression; NA, not available; FAT1, FAT atypical cadherin 1; ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; GBM, glioblastoma multiforme; BC, breast cancer; GC, gastric cancer; CRC, colorectal cancer; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MAPK, mitogen-activated protein kinase; Wnt, wingless/integrated; YAP, Yes-associated protein; NRG1, neuregulin 1; IFN, interferon; GPC3, glypican 3; HGF, hepatocyte growth factor; HIF1α, hypoxia-inducible factor 1 alpha subunit; EGFR, epidermal growth factor receptor; PDCD4, programmed cell death 4; TGF-β1/2, transforming growth factor beta 1/2; CDK, cyclin-dependent kinase; ALDH1A1, aldehyde dehydrogenase 1 family member A1; TFAP2C, transcription Factor AP-2 gamma; AP-1, activator protein 1; CCND1, cyclin D1; MYC, myelocytomatosis oncogene; LEF1, lymphoid enhancer-binding factor 1; ATG4B, autophagy related 4B; SMAD, SMAD family member.

64 patients with AITL found that combinations of mutations in FAT1 with RHOA and KDM5A are associated with poor prognosis. This emphasizes the importance of cell-free DNA as a liquid biopsy in AITL and demonstrates new molecular markers that may help guide molecular diagnosis and treatment plans for patients with AITL (128).

Besides T-cell lymphoma, FAT1 mutations have also been found in B-cell lymphomas (129). Zhao *et al* (130) conducted whole-exome sequencing studies on cases of ocular adnexal mucosa-associated lymphoid tissue lymphoma (OAML) and found that ~10% of the patients had FAT1 gene mutations, indicating that FAT1 may be involved in additional or alternative lymphomagenesis pathways in OAML. In a retrospective study on blastoid or pleomorphic mantle cell lymphoma (B/P-MCL), NGS performed on samples from patients with blastoid and pleomorphic variants was conducted and it was found that FAT1 mutations are one of the most common genetic changes in B/P-MCL. It could be considered that FAT1 mutations may be a pathogenic factor contributing to the aggressive manifestation in patients with mantle cell lymphoma (131).

Studies on multiple myeloma involving FAT1 are relatively rare. Kortüm *et al* (132) designed a targeted gene panel comprising 47 genes to perform a longitudinal analysis of 25 sequential sample pairs, tracking mutational clonal evolution, demonstrating occurrences of FAT1 gene mutations, gains and/or losses in multiple myeloma. In summary, these studies indicate that FAT1 gene mutations may serve an important role in various types of lymphoma and could potentially be used to guide patient prognosis and treatment plans in the future. Further research will serve to improve the understanding of

the specific roles of the FAT1 gene in the development and progression of lymphoma.

## 4. Summary and outlook

FAT1 is a transmembrane protein considered to serve a significant role in the occurrence and development of tumors. The inclusion of a large proportion of studies conducted in China in the present review is primarily due to the increased attention given to the FAT1 gene and the related publications in recent years. However, the pan-cancer analysis data on FAT1 (29,31), including a recent study identifying FAT1 as a target antigen in a subset of *de novo* allograft membranous nephropathy associated with antibody-mediated rejection (133), originate from research conducted worldwide. These studies demonstrate that FAT1 is of interest to the global research community as a therapeutic target and immunotherapy biomarker for various types of cancer. Studies indicate that FAT1 acts as a relay for signals from the extracellular environment to the inside of the cell, regulating various signaling pathways such as Wnt/β-catenin, Hippo and MAPK/ERK, which affect tumor cell proliferation, migration, invasion, stemness and EMT. In addition, FAT1 also serves key roles in precancerous lesions, driving factors, immune escape, tumor microenvironment, drug sensitivity, prognosis, disease monitoring, biomarkers and target development. However, there is still uncertainty regarding the function and clinical significance of FAT1 in tumors. Research on the functional impact of FAT1 mutations and expression levels has shown that FAT1 may exhibit carcinogenic or tumor-suppressive properties in various types of tumors, with specific effects depending on the tumor type (Table I). Although in a large proportion of cases, mutations and expression levels of FAT1 are inversely related, biological functions between mutations and expression levels of FAT1 differ in certain types of tumors, such as HNSCC and ALL. Furthermore, since FAT1 is a large cadherin, there are operational limitations in therapeutic targeting at the protein level and in molecular therapeutic perspectives. Also, as a gene without clearly defined hotspots for mutations, the specific functional changes caused by mutations in FAT1 require further exploration.

The current understanding of FAT1 remains incomplete, particularly concerning the functions of its large extracellular domain. It is still unclear which upstream signals trigger the Wnt, Hippo and MAPK/ERK pathways in relation to FAT1, which receptors are involved in detecting these signals and how the 34 cadherin repeat sequences regulate cell-cell contact. In addition, whether FAT1 primarily acts as an adhesion molecule or a signaling protein and how these functions are coordinated remain to be fully elucidated. Furthermore, the mechanisms that lead to the release and transport of the FAT1 intracellular region to the nucleus, whether FAT1 is localized to mitochondria in cell types other than vascular smooth muscle cells and the impact of FAT1 on cellular metabolism also require further research. The identification of transcription factors and target genes that mediate FAT1 functions and the molecular mechanisms underlying dysregulated FAT1 expression are also key for future investigation. Further research on the aforementioned issues and increasing the understanding of the role of FAT1 in tumor genesis and development may help highlight the importance of FAT1 as a diagnostic, therapeutic and prognostic biomarker and target in clinical applications. These studies will aid in identifying more functions and mechanisms of FAT1, providing more theoretical support for future development of FAT1-based cancer treatment strategies. Although there are no studies focusing on FAT1 small molecule targeted drugs, to the best of our knowledge, the prospects for such drugs targeting FAT1 in the future are promising. The drug binding, metabolic specificity and adverse events of FAT1 small molecule targeted drugs across various organs warrant future investigation. A recent study demonstrated that the tumor suppressor FAT1 is dispensable for normal murine hematopoiesis (134), suggesting that it may be a safe and viable target for therapeutic interventions, particularly in disease contexts where FAT1 is dysregulated or plays a pathogenic role. It is important to address the potential risk of adverse events in various organs when applying anti-molecular targeted drugs systemically, highlighting the need for additional information on the organ-specific reachability of these treatments. Different organs may exhibit varying pharmacokinetics and pharmacodynamics for similar drugs; therefore, the distribution, metabolism and clearance rates of medications in specific organs need to be given special attention.

In conclusion, the current literature demonstrates the potential of FAT1 as a promising therapeutic target. The potential use of FAT1 as a therapeutic target requires further elucidation through research including not only mechanistic *in vitro* investigation, but also through pre-clinical and clinical studies in the future.

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## Authors' contributions

GL and WZ contributed to the conception and design of the study, with GL overseeing the overall direction of the project. GL and WZ also played a key role in formulating the research questions and establishing the scope of the review. GL and WZ supervised the manuscript writing and provided critical guidance throughout the research process. TW and JL contributed to the data analysis, including the synthesis of data from existing studies and the development of the figures. TW was responsible for performing the quantitative and qualitative analyses, while JL provided statistical support and assisted in interpreting the findings. Both TW and JL were instrumental in writing the initial draft of the manuscript and revising the text for clarity and precision. JD played a role in the interpretation of the data, ensuring the results were correctly contextualized within the existing

literature. JD also refined the analysis approach critically, offering suggestions for improving the methodological framework. Additionally, JD contributed to the revision of the manuscript, particularly in areas related to the discussion and conclusions. JD provided feedback on the design and methodology of the review, helping to strengthen the overall structure of the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the study.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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