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Research Progress on the Functional Characteristics, Immune Regulation, and Clinical Significance of the FAT2 Gene in Human Diseases

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Abstract

Background: FAT2 is a member of the atypical cadherin family, characterized by a large extracellular structure and PDZ-binding domains, and is involved in cell adhesion, polarity maintenance, and migration. Recent studies have revealed that FAT2 plays a key role in the development of multiple diseases, particularly tumors and neurological disorders. In various cancers, FAT2 mutations or expression changes are linked to epithelial-mesenchymal transition, immune microenvironment remodeling, and therapeutic response. In the nervous system, FAT2 is essential for synaptic integrity and motor function, with mutations associated with cerebellar ataxia and neurodegeneration. Due to its dual roles in tumor progression and immune regulation, FAT2 has attracted growing interest as a potential biomarker and therapeutic target. This review summarizes the latest findings on the functional roles, regulatory pathways, and clinical significance of FAT2 in human diseases.

Keywords

FAT2, Atypical Cadherin, Tumor Immunology, Nervous System Diseases

1. Introduction

The FAT gene family belongs to the atypical cadherin superfamily, and its mem-

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bers generally have large transmembrane structures, which play a key role in the regulation of cell polarity, migration, proliferation, and histostructuralization [1] [2]. From Drosophila to vertebrates, the Fat adhesin family, as a kind of cross-species adhesion molecule with conserved structure, has retained important biological functions during evolution. In Drosophila, Fat proteins are closely related to morphological construction mechanisms such as planar cell polarity, collective cell migration, and tissue rotation [3]-[6], while in vertebrates, the family has expanded from two genes to four members, FAT1, FAT2, FAT3, and FAT4 [2]-[7]. Phylogenetic analysis revealed that mammalian FAT2 is one of the unique and poorly studied members. In 2006, Katoh systematically identified the gene structure and conserved sequence characteristics of four members of the FAT family by comparative integrated omics analysis, and found that FAT2 encodes a transmembrane protein with 32 cadherin repeats, EGF-like domains, and Laminin G domains. The intracellular tail of FAT2 contains PDZ-binding sites, suggesting that FAT2 may mediate the assembly of multiple signaling complexes [8]. In his subsequent studies, Katoh further explored the function of the FAT family in the occurrence and development of tumors in 2012, and pointed out that although research on FAT2 started late in the FAT family, it has high expression activity in epithelial tissues and may be involved in the regulation of intercellular adhesion [9], polarity maintenance, and tissue remodeling. The function of FAT2 in tumor-related signaling pathways deserves further exploration [10].

In recent years, the biological function of FAT2 has attracted more and more attention, especially in the field of tumor and nervous system diseases [11]. The research published by Feng *et al.* was based on a large-sample analysis from the TCGA and GEO databases, evaluating the expression profiles, prognostic values, and immune-related characteristics of FAT family members in non-small cell lung cancer. The results showed that high expression levels of FAT2 in lung adenocarcinoma patients were associated with better overall survival and were positively correlated with PD-L1 expression, $CD8^+$ T cell infiltration, and TMB, suggesting that it might be a good predictor for immunotherapy [12]. In addition to the tumor background, the function of FAT2 in the central nervous system has also attracted increasing attention. Wang *et al.* reported that FAT2 is highly expressed in the cerebellum and hippocampus by establishing a FAT2 knockout mouse model, using behavioral tests, electrophysiological recordings, and synaptic imaging techniques, and that its loss can lead to reduced synaptic density, abnormal synaptic structure, and defects in motor behavior, confirming that FAT2 is critical for the maintenance of synaptic integrity and neural function [13].

Based on current research progress, although FAT2 was not reported as widely as FAT1 and FAT4 at first, its function in multisystem diseases has gradually emerged [14]-[16]. Based on the latest literature and data, this review aims to systematically summarize the structural features, biological mechanisms, signaling pathway regulation, and immunomodulatory effects of FAT2, its clinical significance in cancer and nervous system diseases, and explore its research value as a potential biomarker and therapeutic target.

2. Structure and Biological Characteristics of the FAT2 Gene

The protein encoded by the FAT2 gene is a large transmembrane cadherin with a complex structure, which contains 32 cadherin repeats, multiple EGF-like domains, and a Laminin G-like domain. The intracellular tail contains PDZ-binding sites and potential phosphorylation sites, suggesting that it is not only responsible for intercellular adhesion. It may also participate in the regulation of a variety of signaling pathways by interacting with intracellular signaling complexes [2]. In 2006, Katoh systematically compared the similarity and specificity of the gene structure of each member of the FAT family using integrated comparative genomics methods and, for the first time, clearly defined the composition of the conserved domain and the transmembrane characteristics of FAT2 [8]. On this basis, Katoh further summarized the structural information and potential functions of FAT2 in 2012. He pointed out that, compared with other FAT family members, FAT2 has more significant extracellular structural repeat expansion and the possibility of endogenous signal transduction, and that its function may depend on the precise binding of its domain with ligands and signaling molecules [10].

In terms of tissue distribution, FAT2 is not only expressed in epithelial tissues but also shows a significant expression advantage in the nervous system. Based on the public expression profile database and immunohistochemical results, Zhang *et al.* conducted a review analysis in 2016 and pointed out that FAT2 was highly expressed in the cerebellum, ganglion cells, and cortical neurons, and that its expression pattern was closely related to the neural development time course and the synaptic maturation process [17]. Wang *et al.*, in 2025, provided more direct experimental evidence by creating FAT2 gene knockout mice and combining behavioral tests, tissue immunostaining, synaptic ultrastructure observation, and other means. FAT2 deficiency results in reduced synaptic density, disordered neuronal distribution, and significant motor coordination disorders in the cerebellum and hippocampus, indicating that FAT2 not only plays a role in the maintenance of synaptic structure but also participates in the stability of neural electrical activity and behavioral regulation [13].

In terms of cellular functions, FAT2 has been shown to play a key role in the maintenance of epithelial cell polarity and collective migration. In a study of Wnt/PCP-related factors, researchers found that FAT2 has a localization and functional interaction with the cell surface receptor Lar and the secretory chemotactic molecule Sema5c. The regulatory mechanism of FAT2 further affects the orderly movement and tissue morphogenesis of collective epithelial cells by regulating the polar distribution of these molecules. This process is considered to be one of the important mechanisms of epithelial development and regeneration [18]. Taken together, FAT2 not only shows complex and multifunctional potential in structure but also shows highly systematic expression and functional regulation in tissues. Fat2 may act as the upstream regulatory node of multiple signaling pathways and have important biological significance in maintaining cell polarity,

neural synaptic integrity, and tissue migration dynamics.

3. Mutational Profile and Expression Profile of FAT2 in Tumors

3.1. Non-Small Cell Lung Cancer (NSCLC)

In non-small cell lung cancer (NSCLC), FAT2 gene mutation status is closely related to tumor immunophenotype and immunotherapy response. Feng *et al.*'s study in 2022 was based on the TCGA database. The analysis showed that the mutation frequency of FAT2 in lung adenocarcinoma (LUAD) was 9.8%, and that in lung squamous cell carcinoma (LUSC) was 6.3%. Lung adenocarcinoma patients with FAT2 mutations had a higher expression level of PD-L1, accompanied by significant infiltration of immune cells such as $CD8^+$T cells, M1 macrophages, activated memory $CD4^+$T cells and follicular helper T cells, showing the characteristics of "immune fever" tumors [12]. Another study in patients with NSCLC found that patients with co-mutations in the FAT family (including FAT2) and LRP1B had a significantly higher tumor mutation burden (TMB) (17.05 mut/Mb), and patients with such co-mutations were more likely to benefit from immunotherapy. These findings suggest that FAT2 mutations may participate in the regulation of immunotherapy response by affecting the tumor immune microenvironment [19]. In the analysis of TCGA and MSKCC multi-omics databases for lung cancer, researchers compared the gene mutation spectrum of NSCLC patients aged ≤40 years and ≥60 years, and found that the frequency of FAT2 mutation was significantly higher in elderly patients [20]. In addition, Wu *et al.* conducted a large-scale targeted sequencing analysis of 2025 Chinese patients with lung adenocarcinoma (LUAD) and found that FAT2 mutation was significantly enriched in elderly patients aged 70 years and older, and it was one of the 20 age-related high-frequency mutated genes (co-occurrence with FAT1, KEAP1, MTOR, etc.) [21] [22]. These findings suggest that FAT2 may be closely related to age-related characteristics of tumor progression, and its mutation status can be used as a potential molecular classification basis for immunotherapy, especially in the elderly patient population. At the protein level, Shames *et al.* (2012) used a combination of microarray screening and functional validation to identify FAT2 as one of the potential cell-surface markers that is significantly upregulated in lung squamous-cell carcinoma, showing significant differences from normal lung tissue. This finding indicates that FAT2 is not only significant at the level of gene mutation, but may also be a candidate target for targeted immune or molecular probes [23]. Further evidence-based study was proposed by Rao *et al.* In 2023, the research team selected 35 patients with stage I lung adenocarcinoma. By targeted sequencing of tumor tissues and paired normal tissues of patients with rapid recurrence within 1 year after surgery and those without recurrence for more than 3 years after surgery, it was found that the mutation frequency of FAT2 in this population reached 11.4%. FAT2 is one of the 13 commonly mutated genes. Among these mutations, FAT2 showed a significant co-mutation trend with

MLL3 and MED12 ($p \approx 0.056$), and the tumor mutation burden (TMB) of patients with FAT2 mutation was significantly increased ($p < 0.05$), suggesting that FAT2 may participate in the regulation of recurrence risk by promoting gene instability in early LUAD. Although immunohistochemistry analysis of FAT2 protein expression was not performed due to antibody deficiency, its mutation was included in the analysis of recurrence correlation, reflecting its potential value in the molecular progression of stage I LUAD [24]. FAT2 has also been identified as a potential key gene in cancer risk regulation studies involving smoking exposure. Tang *et al.* systematically evaluated the interaction effect of genetic factors and smoking on the risk of pancreatic cancer based on the GWAS data of PanScan, PanC4 and other pan-cancer cohorts, combined with the stratification variables of smoking amount and principal component analysis (PCA) modeling. Multiple candidate pathways and genes were screened by nested likelihood ratio test (LRT). FAT2 was selected as one of the top nine significant interaction genes with Pinteraction < 0.0005, suggesting that FAT2 may play an important role in tobacco exposure-related carcinogenesis. By Ingenuity Pathway Analysis, FAT2 was classified into Axonal Guidance Signaling, which is considered to be one of the central pathways in smoking-related cancer susceptibility. Although this study focused on pancreatic cancer, FAT2, as a member of the FAT family involved in the regulation of cell adhesion and migration, may have a potential function in smoke-related lung cancer that deserves further exploration [25].

In conclusion, although the frequency of FAT2 mutation in NSCLC is not high (less than 10%), its mutation status can affect the tumor immunophenotype and the response of patients to immunotherapy by regulating the expression of immune checkpoint molecules and immune cell infiltration, which provides a potential biomarker for precision immunotherapy of NSCLC.

3.2. Esophageal Squamous Cell Carcinoma (ESCC)

The FAT2 gene mutation has a certain frequency in esophageal squamous cell carcinoma (ESCC), and its mutation status is related to the occurrence and development of ESCC. Based on the Japanese Cancer Genome Atlas (JCGA), Booka *et al.* performed whole-exome sequencing and in-depth validation on ESCC samples from 44 Japanese patients in 2021 and found that FAT2 mutations were mainly missense mutations. In addition, the overall survival rate of patients with FAT2 mutation was significantly lower than that of wild-type patients ($p < 0.05$), suggesting that this gene mutation may participate in the process of tumor formation by destroying cell adhesion function or affecting the maintenance of epithelial cell polarity and differentiation regulation [26]. This result is further supported by another study on the genomic characteristics of ESCC. A systematic analysis of 139 ESCC samples identified FAT2 as one of the significantly mutated genes, indicating that truncating mutations in the FAT family (including FAT2) occur frequently in ESCC. Moreover, the mutations of FAT1 and FAT3 are mutually exclusive, suggesting that FAT2 may act as a tumor suppressor and participate in

the occurrence and development of ESCC by regulating cell-cell interactions [27].

In summary, although FAT2 is not the most frequently mutated gene in ESCC, its mutation pattern and functional association make it a noteworthy molecular event in this cancer and provide important clues for understanding the pathogenesis of ESCC.

3.3. Gastric Cancer (STAD)

In gastric cancer (STAD), FAT2 expression was significantly correlated with tumor invasiveness. In 2017, Li *et al.* performed immunohistochemistry and survival analysis on 98 gastric cancer tissues and found that high expression of FAT2 was significantly associated with lymph node metastasis, TNM stage progression, and poor overall survival of patients, and that it was still an independent poor prognostic factor in the multivariate Cox regression model. It is suggested that FAT2 may play a carcinogenic role in the progression of gastric cancer [28]. Further mechanistic study was proposed by Zhou *et al.* In 2021, based on ceRNA regulatory network analysis, they found that the RP11-21C4.1-SVEP1 gene pair was significantly related in the FAT2 mutation background and may regulate the expression of tumor migration-related genes by affecting the lncRNA-miRNA-mRNA axis and participate in the malignant progression of gastric cancer [29]. In another large-sample and multidimensional analysis study, Wang *et al.* systematically evaluated the role of FAT family gene mutations in the prognosis of patients with gastric adenocarcinoma (STAD) in 2022. The study integrated gene mutations, clinical data, and survival data from the TCGA gastric cancer cohort, and constructed an association model between FAT mutations and prognosis through bioinformatics methods. The results showed that, among all FAT family members, FAT2 mutations were significantly associated with longer overall survival (log-rank p-value < 0.05), which provided support for the potential tumor suppressor function of this gene. The researchers further analyzed the differences in immune cell infiltration, immune checkpoint expression, and pathway enrichment between FAT2-mutant patients and wild-type patients, and found that the expression of T cells, NK cells, and antigen presentation-related genes in the FAT2-mutant group were up-regulated, suggesting that FAT2 may achieve better survival prognosis by improving the tumor immune microenvironment. Combined with GSEA enrichment analysis, FAT2 mutation was found to be closely related to the Wnt signaling pathway, the TGF-β signaling pathway, and the cell adhesion molecule pathway, further supporting its key role in regulating tumor behavior from the mechanism. These results not only enhance the evidence base for the functional localization of FAT2 in STAD, but also provide multi-omics support for its use as a prognostic biomarker [30]. In the immune score model involving PPAR signaling, researchers found that the frequency of FAT2 mutation was significantly increased in the high PPARA/PPARG expression group and was associated with high immune score and increased TMB, suggesting that FAT2 may be involved in the regulation of the immune microenvironment of gastric adenocarcinoma, but its direct rela-

tionship with prognosis still needs to be further verified [31].

3.4. Colorectal Cancer (CRC)

In colorectal cancer (CRC), FAT2 mutations are thought to be strongly associated with a subtype with distinct immune profiles. Wang *et al.* analyzed multiple large-scale colorectal cancer sequencing datasets in 2022 and found that FAT family mutations, represented by FAT2, constitute an underappreciated molecular subtype of colorectal adenocarcinoma that exhibits increased microsatellite instability (MSI-H) and immune activation signatures. This suggests that FAT2 may enhance tumor immune sensitivity by enhancing antigen presentation and immune recognition [30]. This conclusion is consistent with the study by Xie *et al.* (2014), which was based on a whole-genome comparison between primary and metastatic tumors, and found that the mutation frequency and copy number changes in FAT2 in metastatic CRC were significant, suggesting that FAT2 may play a role in the formation of tumor metastatic potential [32].

3.5. Endometrial Carcinoma (UCEC)

In endometrial cancer (UCEC), FAT2 mutations also exhibit immune-related characteristics. Wang *et al.*, in 2023, in a study on predictive markers for immunotherapy, pointed out that FAT2 mutations are highly enriched in the MSI-H patient population and are co-expressed with genes related to the programmed death protein pathway. The research showed that patients with FAT2 mutations responded well to immune checkpoint inhibitors (ICIs) treatment and had significantly better survival outcomes than wild-type patients, suggesting that FAT2 may serve as a predictive factor for the benefit of immunotherapy in endometrial cancer [33].

3.6. Acute Myeloid Leukemia (AML)

In hematological malignancies, FAT2 has also been incorporated into key molecular models for survival prediction. In 2020, Zhuang *et al.* integrated multi-omics data from TCGA, including transcriptome, mutation, and methylation profiles, to identify 10 key genes closely associated with the prognosis of acute myeloid leukemia (AML), among which FAT2 was included. They further established a survival risk scoring system for AML patients based on the LASSO regression model and validated its robustness in multiple independent cohorts, suggesting that FAT2 may not only have regulatory functions in solid tumors but also play a significant role in hematological malignancies [34].

3.7. FAT2 Mutations in Rare or Low-Incidence Cancers

In addition to mainstream solid tumors, FAT2 mutations have also been found in many rare or low-incidence cancers, suggesting that FAT2 may be widely involved in the occurrence and development of a variety of tumors. In laryngeal squamous cell carcinoma (LSCC), case studies have reported a FAT2 missense mutation in

an 18-year-old HPV45-positive female patient, while another HPV31-positive patient had no mutation, although the sample size was limited, suggesting that it may have a potential link with tumorigenesis related to specific viral subtypes [35]. In a rare case of PEComa reported in 2024, the patient had liver and kidney lesions, and a c.5986C > T (p. H1996Y) mutation of the FAT2 gene was detected in renal tissue. The patient was also associated with TSC, but no TSC1 or TSC2 mutations were detected, suggesting that FAT2 may play a potential pathogenic role in this type of TSC-negative PEComa [36]. FAT2 has also been identified as one of the frequently mutated genes in eccrine porocarcinoma (EP), a rare cutaneous adenogenic malignant tumor. Denisova *et al.* performed whole-exome sequencing on 14 primary EP tumor samples in 2022 and found that FAT2 had nonsynonymous mutations in six samples, and its mutation frequency was classified as the most common gene mutation together with TP53 [26]. Studies have shown that FAT2, as an atypical cadherin, may be involved in the regulation of the Hippo pathway and the maintenance of cell polarity. Its mutation may affect the stability of epithelial structure and signal transduction, thus playing an important role in the development of EP. These results suggest that FAT2 not only plays a pathogenic role in common solid tumors, but also may have a potential driver function in rare tumors derived from skin appendages, which provides clues for further exploration of its mechanism. In a genome-wide study of HBV-associated intrahepatic cholangiocarcinoma (iCCA), researchers found that FAT2 was one of the secondary hotspots of HBV integration (5/108 cases), and the integration events mainly occurred in the intron region. Studies have shown that these integrations are associated with the activation of the epithelial-mesenchymal transition (EMT) pathway, suggesting that FAT2 may be involved in the progression of iCCA [37]. Although most of the studies on FAT2 in this low-incidence tumor are still case reports or preliminary observations, its mutation or integration events suggest that FAT2 may have a pathogenic role in specific molecular subtypes, which provides potential clues for future mechanism research and accurate classification.

Table 1. Summary of FAT2 mutation features in human cancers.

Cancer Type	Mutation Frequency	Immune Features	Prognostic Impact
NSCLC (LUAD/LUSC)	LUAD: 9.8%, LUSC: 6.3%	↑ PD-L1, $CD8^+$, M1 macrophages; ↑ TMB; immune-hot	Better ICI response; ↑ recurrence risk in early LUAD with co-mutations
Esophageal Squamous Cell Carcinoma (ESCC)	Detected in 44 Japanese ESCC samples (JCGA); truncating/missense	N/A	↓ Overall survival with FAT2 mutation
Gastric Cancer (STAD)	Detected (WES/IHC); associated with TNM and lymph metastasis	↑ Immune score, T cells, NK cells; enriched in Wnt/TGF-β pathways	Mixed: High expression → worse OS; mutation → better OS
Colorectal Cancer (CRC)	Detected (MSI-H subtype); associated with metastasis	↑ Immune activation signature; ↑ MSI-H	Suggests immune-sensitive subtype; role in metastasis

Continued

Endometrial Carcinoma (UCEC)	Enriched in MSI-H subtype; co-expressed with PD-pathway	↑ PD-L1, ↑ T-cell signaling; good ICI response	FAT2 mutation → longer PFS; good response marker
Acute Myeloid Leukemia (AML)	Included in 10-gene survival model (TCGA AML)	N/A	High-risk gene; poor survival in AML
Rare/Low-Incidence Cancers (e.g. LSCC, PEComa, EP, iCCA)	Detected in case studies and small cohorts	Variable—HBV integration (iCCA), possible Hippo/PCP involvement	Potential pathogenic/driver role in specific cases

Taken together, the mutation spectrum and expression characteristics of FAT2 in tumors show high heterogeneity, and its function can exhibit bidirectional effects—tumor promotion or suppression—depending on the cancer background, suggesting that FAT2 is not only a potential regulator of tumor development and progression but also an important biomarker for tumor classification and treatment response prediction (Table 1).

4. Function of FAT2 in Nervous System Diseases

4.1. Cerebellar Ataxia (SCA)

In the central nervous system, FAT2 not only participates in neural development as a structural adhesion molecule, but its mutation is also closely related to the pathogenesis of a variety of nervous system diseases. FAT2 has been identified as one of the key pathogenic genes in autosomal dominant spinocerebellar ataxia (SCA). Studies have shown that FAT2 mutations can lead to neuronal migration disorders and incomplete synaptic structure, resulting in motor coordination defects and progressive dyskinesia. Wang *et al.* performed systematic experiments using a FAT2 gene knockout mouse model in 2025 to confirm that FAT2 plays an irreplaceable role in maintaining the synaptic density and morphological integrity of Purkinje cells in the cerebellum by behavioral tests, electrophysiological recordings, and ultrastructural microscopic imaging. The loss of FAT2 can lead to sparse synaptic connections, decreased neurotransmitter release efficiency, and can exhibit typical SCA symptoms such as motor coordination disorder and imbalance, which clarify the physiological function of FAT2 in neurodevelopment [13]. In another retrospective study of the molecular mechanism of inherited cerebellar ataxia, researchers pooled multiple genes responsible for SCAR and SCA and showed that FAT2 mutations mainly occurred in the form of missense or splice-site variants that disrupted its role in axon guidance and synaptic junction formation. This study has further deepened the understanding of the pathogenic pathway of this disease [38].

4.2. Meningioma

In meningioma studies, FAT2 has also been found to harbor potential pathogenic mutations. A missense mutation, c. 3597G > C, in the extracellular domain of FAT2 was reported in a whole-exome sequencing study of patients with spinal

meningioma; this mutation may interfere with the interaction of FAT2 with the core components of the Wnt/PCP pathway, thereby affecting cell polarity maintenance and tissue structure stability. Studies have speculated that this mutation may activate the atypical Hippo signaling axis by destroying the intercellular adhesion and polarity control mechanism and promote the abnormal proliferation and invasion of tumor cells, suggesting that the function of FAT2 in meningiomas needs to be further verified [39].

4.3. Progressive Supranuclear Palsy (PSP)

In progressive supranuclear palsy (PSP), the change in FAT2 expression provides a potential biomarker clue for disease diagnosis. A proteomic study based on 120 cerebrospinal fluid samples (40 PSP patients, 40 PD patients, and 40 healthy controls) showed that FAT2 was significantly downregulated in the cerebrospinal fluid of PSP patients, and its expression level was lower than that of PD patients and healthy controls. Based on tandem mass tag (TMT) quantitative mass spectrometry and receiver operating characteristic (ROC) curve analysis, we found that the area under the curve (AUC) of FAT2 was 0.810, which had a certain sensitivity and specificity in differentiating PSP from other control biomarkers. These findings suggest that FAT2 may be involved in PSP-related neurodegenerative processes (such as axon-dendritic contact regulation). This finding provides a new perspective for understanding the molecular mechanism of PSP and also lays the foundation for further investigation of it as a potential diagnostic marker in CSF [40].

5. Signaling Pathway and Functional Mechanism of FAT2

FAT2 plays a multifunctional regulatory role in multiple signaling pathways, and its mechanism of action involves multiple aspects, such as cell migration, polarity maintenance, and transcriptional program remodeling. During the epithelial-mesenchymal transition (EMT), Dang *et al.* in 2016, through gain-of-function and loss-of-function experiments in human head and neck squamous cell carcinoma cell lines, revealed that ΔNp63α can directly transcribe and activate FAT2 and simultaneously induce the expression of the transcription factor Slug, thereby enhancing the migration and invasion abilities of tumor cells. The study verified the binding ability of ΔNp63α to the FAT2 promoter region through chromatin immunoprecipitation (ChIP) combined with qPCR analysis and further confirmed its mediating role in promoting the EMT process through FAT2 knockout rescue experiments [41].

In the atypical Wnt/planar cell polarity (PCP) pathway, FAT2 also plays a key role in localization regulation. Using a Drosophila epithelial collective migration model and mammalian cell polarity experiments, we observed that FAT2 maintains tissue planar orientation alignment by limiting the subcellular localization of cell polarity regulators Lar and Sema5c to coordinate the synchronized changes in polarity between cells during collective migration. Loss of FAT2 can cause dis-

turbance of the PCP pathway and induce disruption of migration patterns, suggesting its decisive role in collective cell motility and directional migration [18]. Li *et al.* systematically evaluated the role of FAT2 in tumor cell migration by applying siRNA technology to knock down the expression of FAT2 in HSC-1 human cutaneous squamous cell carcinoma cells in 2008. The results showed that FAT2 deficiency significantly inhibited cell Transwell migration, scratch healing rate, and protrusion formation in a gold gel assay, suggesting that FAT2 is essential for the maintenance of filopodia structures at the leading edge. Immunofluorescence and cell tracking analysis were used to confirm the direct function of FAT2 in cytoskeleton remodeling and polar migration, which provided an important functional experimental basis for the role of FAT2 in the formation of a tumor invasive phenotype [42]. Although FAT1 and FAT4 have been extensively characterized as upstream regulators of the Hippo signaling pathway—particularly through modulation of LATS1/2-mediated YAP phosphorylation—no primary studies to date have directly demonstrated a physical or functional interaction between FAT2 and canonical Hippo pathway components. Current literature provides only indirect clues suggesting FAT2's involvement in this pathway. For instance, Li *et al.* [32] reported that in intrahepatic cholangiocarcinoma, HBV integration at the FAT2 locus was associated with transcriptional activation of gene networks related to planar cell polarity (PCP) and Hippo signaling. Additionally, pathway enrichment analyses of FAT2-mutant tumors in both lung and gastric cancers revealed significant alterations in Hippo-related gene sets [12] [19], though these findings remain correlative and lack direct mechanistic evidence.

Given its structural similarity to other FAT family cadherins and its role in cytoskeletal regulation and cell polarity, FAT2 is hypothesized to influence YAP/TAZ subcellular localization in a context-dependent manner. Wang *et al.* [13] observed altered synaptic morphology and postsynaptic density protein expression in FAT2-knockout mice generated in 2025, suggesting potential crosstalk between FAT2 and adhesion-regulated YAP/TAZ signaling. Furthermore, in a mutational analysis of meningioma, FAT2 missense mutations were proposed to disrupt interactions with polarity-regulating pathways, implying FAT2's role in modulating structural dynamics via PCP and Hippo signaling [39]. Supporting this view, Katoh [10] previously proposed that FAT cadherins may regulate YAP/TAZ nuclear localization and phosphorylation indirectly through interaction of their intracellular domains with Hippo components such as LATS1/2 or MST1/2. Nevertheless, in the absence of direct experimental validation—such as co-immunoprecipitation or functional knockout models—the FAT2-Hippo/YAP axis remains a speculative but biologically plausible mechanism worthy of further investigation.

In terms of non-coding RNA regulation, Zhou *et al.* carried out ceRNA network construction based on TCGA data of gastric cancer in 2021 and found that the RP11-21C4.1 and SVEP1 gene pair was significantly co-expressed in the FAT2 mutant high expression subgroup. Based on the combination of bioinformatics prediction and experimental data, the lncRNA-miRNA-mRNA axis has been pro-

posed to relieve the inhibition of SVEP1 and FAT2 by adsorbing miR-1295-5p, and to positively regulate tumor migration and epithelial adhesion-related factors. This regulatory mechanism suggests that FAT2 may not only be activated downstream of the pathway but may also form a feedback regulatory network with non-coding RNA to participate in the regulation of cancer cell malignant behavior [29].

In malignant glioma, FAT2 has also been confirmed to be involved in signaling regulation mechanisms during the formation of chemotherapy resistance. Rabe *et al.* (2022) identified a set of signature genes associated with the persister state, including FAT2, CHI3L1, KLK5, and HB-EGF, using a TMZ treatment model of U251 glioma cells. Studies have found that the proteins encoded by these genes are located in the extracellular space or cell membrane, are involved in cell-cell interactions and extracellular matrix remodeling, and may jointly regulate the survival ability of tumor cells under drug pressure. Single-cell transcriptional analysis showed that FAT2 was heterogeneously expressed in different drug-resistant cells, and its expression was upregulated after 4 days of treatment. The expression of FAT2 is affected by CHI3L1 and KLK5, and the silencing of FAT2 also inhibits the expression of KLK5 and CHI3L1, suggesting that they may be in a positive feedback co-regulatory network. In addition, knockdown of FAT2 reduced the basal cell survival rate in the absence of drug treatment, suggesting that FAT2 plays a key role in cell homeostasis and drug resistance. These results support that FAT2 is not only a migration and polarity regulator but may also be involved in the signal regulation and drug resistance acquisition process under stress by mediating cell-cell and cell-cell signaling interactions [43].

Taken together, these findings demonstrate the functional diversity of FAT2 as a transmembrane adhesion protein in multiple key signaling pathways. Fat2 is not only involved in the regulation of cell migration and polarity but may also participate in YAP/TAZ activation and the non-coding RNA regulatory network, playing a central signaling regulatory role in multiple physiological and pathological environments.

6. Immunomodulatory Role and Clinical Significance of FAT2

FAT2 plays an important role in the regulation of the tumor immune microenvironment. Its mutation status is closely related to immune cell infiltration, immune-related signal expression, and immunotherapy response. Feng *et al.* conducted a systematic analysis of the expression and mutation characteristics of FAT family members in non-small cell lung cancer (NSCLC) in 2022. TCGA data and multiple GEO independent cohorts were used for immune infiltration annotation and multivariate Cox regression modeling. FAT2 mutation was found to be significantly associated with enhanced infiltration of $CD8^+$ T cells, $CD4^+$ memory T cells, and M1 macrophages, showing characteristics of high immune activation. Immune-related pathway analysis revealed that FAT2 mutation was accompanied by the up-regulation of multiple immune activation signals (such as IFN-γ response, antigen presentation, and chemokine signaling), suggesting that FAT2

mutation plays a key role in regulating the tumor immune microenvironment. It was further shown that PD-L1 expression level and tumor mutation burden (TMB) were significantly increased in FAT2 mutant samples, supporting its potential value as a tumor classification marker of "immune fever" [12]. This finding was also confirmed in independent lung cancer clinical samples. Using targeted next-generation sequencing and retrospective evaluation of immunotherapy response in a non-small-cell lung cancer cohort, Wang *et al.* observed that FAT2 mutations were significantly enriched in the immunotherapy responder population, and their mutation status was positively correlated with higher TMB, PD-L1 expression, and $CD8^+$ cell infiltration. Researchers have proposed that FAT2 mutations may synergistically promote tumor immune recognition and clearance by affecting cell adhesion structures and increasing immunogenicity, thus showing better survival outcomes in patients treated with immune checkpoint inhibitors [19]. In endometrial cancer (UCEC), the study by Wang *et al.* in 2023 showed that the FAT2 mutation population was highly distributed in a microsatellite instability high (MSI-H) background, accompanied by high PD-L1 expression and activation of T-cell inflammatory signaling, suggesting that it may enhance immunotherapy response in this subtype. Survival analysis using the TCGA-UCEC data showed that FAT2 mutation status significantly prolonged the progression-free survival of patients and had a good independent prognostic value. This study supports FAT2 as a predictive marker for immunotherapy response in uterine cancer and proposes that there is a synergistic activation mechanism between FAT2 and the core pathways of immune response [33]. In contrast to the above benign effects, the expression characteristics of FAT2 in gastric cancer are negatively correlated with the prognosis of patients. Li *et al.* conducted a study based on gastric cancer tissue microarray and clinical follow-up in 2017 and found that the high expression of FAT2 was significantly correlated with the depth of tumor invasion, the number of lymph node metastases, and TNM stage. By immunohistochemistry score and Cox multivariate analysis, FAT2 was identified as an independent adverse prognostic factor. Its high expression can predict shorter overall survival and an increased risk of recurrence, and may mediate the formation of an invasive phenotype by enhancing the adhesion and migration abilities of tumor cells [28].

Taken together, these findings suggest that the prognostic impact of FAT2 is modulated by tumor-specific downstream signaling cascades and immune microenvironmental characteristics. In non-small cell lung cancer (NSCLC) and endometrial carcinoma (UCEC), FAT2 mutations are frequently associated with high tumor mutational burden (TMB), microsatellite instability-high (MSI-H) status, and increased infiltration of $CD8^+$ T cells and M1 macrophages, features indicative of an "immune-hot" phenotype and improved responsiveness to immune checkpoint inhibitors (ICIs) [12] [19] [33]. In these settings, FAT2 mutations appear to activate key immune pathways, such as interferon-γ signaling, chemokine expression, and antigen presentation, enhancing antitumor immune surveillance and contributing to better clinical outcomes.

In contrast, in gastric cancer (STAD), FAT2 is primarily upregulated at the protein level rather than mutated, and its high expression correlates with increased tumor invasion, lymph node metastasis, and poor overall survival [26]. Mechanistic studies suggest that FAT2 may promote epithelial-mesenchymal transition (EMT), cytoskeletal remodeling, and tumor cell migration through Wnt, TGF-β, and cell adhesion molecule pathways [29]-[31]. Additionally, the immunosuppressive tumor microenvironment often seen in gastric cancer may further diminish the potential immune-activating role of FAT2, instead favoring its function in promoting tumor progression.

Therefore, the bidirectional prognostic implications of FAT2 across cancer types may reflect distinct molecular wiring and immune contexts. FAT2 may act as an immune-enhancing tumor suppressor in immunogenic tumors such as NSCLC and UCEC, but function as a pro-invasive oncogenic factor in tumors like STAD that are dominated by stromal and invasive signaling. These findings underscore the importance of considering tumor-specific signaling and immune profiles when interpreting FAT2-related molecular events in clinical oncology.

7. Prospects and Challenges

As an atypical cadherin, FAT2's function in a variety of tumors and nervous system diseases has been gradually revealed, but its specific molecular mechanism and cross-pathway integration ability have not been fully elucidated. Katoh proposed in a systematic review in 2012 that FAT2 may couple with the core kinases of the Hippo signaling axis, such as LATS1/2 and MST1/2, through its intracellular domain. However, compared with FAT1 and FAT4, the direct relationship between FAT2 and these pathways has not been experimentally verified. Studies have highlighted the potential of FAT2 in signal integration, especially in the regulation of cell adhesion and polarity. There is still an important knowledge gap regarding whether FAT2 is involved in the activation of the transcription factors YAP/TAZ and their trans-nuclear localization regulation [10]. Wang *et al.* observed synaptic dysfunction and dyskinesia in FAT2 knockout mice in 2025, suggesting that FAT2 may participate in the establishment of cell polarity in the nervous system by regulating cytoskeletal- and adhesive-related signaling; however, direct evidence is still lacking to determine whether FAT2 affects the STAT or TGF-β signaling pathways. Animal models and three-dimensional organoid platforms with stable expression or inactivation of FAT2 have not been established in existing studies, which limits functional analysis and the development of targeted intervention strategies to a certain extent [13]. From a clinical perspective, the expression pattern, mutation characteristics, and immune correlation of FAT2 in multiple cancers suggest its potential as a three-dimensional integrated function-immune-prognosis marker. Wang *et al.* found that FAT2 mutation predicted a good response to immune checkpoint inhibitors in endometrial cancer patients in 2023, while Feng *et al.* further verified its positive correlation with TMB, PD-L1, immune infiltration, and other indicators in the NSCLC cohort. Both studies in-

dicated that FAT2 mutation or expression status can be used as a predictive tool for immunotherapy response and have shown unique predictive ability in different tumor types. However, due to the limitations of sample size and disease distribution, its cross-cancer versatility and adaptation need to be systematically verified in larger sample sizes and multicenter cohorts [12] [33]. Current therapeutic concepts targeting FAT2 primarily fall into two categories: modulating its expression in tumor cells and leveraging FAT2 mutation status as a predictive biomarker for immunotherapy. Strategies such as RNA interference (RNAi) or CRISPR-based repression to inhibit FAT2 expression in invasive tumors are conceptually promising, especially in cancers like gastric adenocarcinoma, where FAT2 promotes metastasis [28] [29]. However, these approaches face delivery challenges and potential off-target effects due to the broad tissue distribution of cadherins [2]. On the other hand, in tumors where FAT2 mutation correlates with immune activation (e.g., NSCLC, UCEC), FAT2 alteration may serve as a selection criterion for immune checkpoint inhibitor (ICI) therapy [12] [19]. Nevertheless, a major hurdle is the lack of validated, tumor-type-specific functional assays to define FAT2's role as either oncogenic or tumor-suppressive, making patient stratification and drug development inherently complex [10] [32]. Together, these findings emphasize the promising yet challenging nature of FAT2 as a therapeutic and prognostic target. Continued efforts in mechanistic elucidation, cross-cancer validation, and precision intervention development will be essential to fully realize its translational potential.

Authors' Contributions

Xiaoyue Deng: Writing-original draft, Visualization. Weihua Hu edited the manuscript. All authors reviewed the manuscript.

Conflicts of Interest

The authors declare no competing interests.

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