REVIEW

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Molecular Mechanisms of FAT Atypical Cadherin 1 (FAT1), the Hippo Pathway, and the Yes-Associated Protein (YAP) Signaling Pathways in Some Cancers

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Abstract

Introuduction: FAT atypical cadherin 1 (FAT1), the Hippo pathway and Yes-associated protein (YAP) signaling play significant roles in cell proliferation, differentiation, and apoptosis. Dysregulation of these pathways contributes to tumorigenesis in multiple cancers, including head and neck squamous cell carcinoma (HNSCC), hepatocellular carcinoma (HCC), and breast cancer. **Methods:** The *FAT atypical cadherin 1* (*FAT1*) gene is an ortholog of the Drosophila fat gene, which encodes the protocadherin FAT1. *FAT1* is one of the most mutated genes and is therefore considered to be an emerging cancer biomarker and a potential therapeutic target for novel therapies. However, the molecular mechanisms of the FAT1 signaling pathways it mediates has not been fully elucidated. **Results:** The Hippo-YAP pathway is considered a crucial oncogenic pathway in multiple tumors. The expression of genes controlled by the Hippo downstream transcriptional coactivators Yes-associated protein 1 (YAP) is widely deregulated in different human cancers, including head and neck squamous cell carcinoma (HNSCC). **Conclusion:** This review discusses the *FAT1*, *Hippo* and *Yap* genes, with a focus on their mutations and expression levels, and their impact on signaling pathways and mechanisms in various types of cancer.

Keywords: STAT3- Wnt/β-catenin- EGFR family- HER

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Introduction

FAT atypical cadherin 1 (FAT1) is a member of the FAT family of cadherins and is known for its large extracellular domain and cytoplasmic tail, which interact with intracellular signaling pathways. Its key functions include cell adhesion, regulation of the actin cytoskeleton, and tumor suppression through the modulation of Hippo signaling and inhibition of Hippo/Yes-associated protein (YAP) pathway activation.

FAT1 plays different roles in different tissues or cancer types, it is considered an oncogene in cancers such as acute leukemia, hepatocellular carcinoma (HCC), glioblastoma (GMB), and gastric cancer; but is a tumor suppressor gene in *HNSCC*, *ESCC*, breast cancer, and cervical cancer [1]. The effect of *FAT1* mutation on malignant phenotypes has not been investigated, and there is a paucity of knowledge about its clinical implications.

Physiological role of FAT1 as an adhesion molecule

The *FAT1* gene was first cloned from the human T-cell acute lymphoblastic leukemia (T-ALL) cell line and is located on chromosome 4q34-35 which consists of 27 exons [2]. FAT1 is a member of the cadherin-like protein family and is a transmembrane protein that encodes 4588 amino acid residues. It consists of 34 cadherin repeats, a laminin G domain, and five epidermal growth factor (EGF)-like repeats in the extracellular region, followed by a transmembrane region. Its C-terminal cytoplasmic tail contains a PDZ-binding motif [2] (Figure 1). Under normal physiological conditions, FAT1 is considered as a molecular "brake" during mitochondrial respiration [3], therefore, it controls the proliferation and migration of vascular smooth muscle cells during injury [4]. Moreover, it functions as a receptor during signaling pathways that regulate cell–cell interactions and planar cell polarity [5] The *FAT1* gene is considered a transcriptional activator that binds elements that code with NFκB and E2F1 in its

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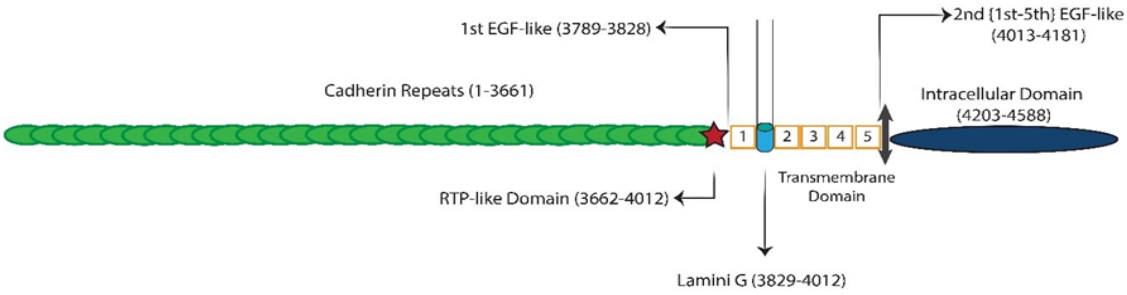

Figure 1. Diagrammatic Illustration of FAT1's Domain Architecture. Multiple cadherin repeats (amino acids 1–3661) found in the extracellular area mediate structural connections and cell–cell adhesion. An RTP-like domain (3662–4012) and a Laminin G-like domain (3829–4012) that support signaling regulation and protein–protein interactions come next. The first EGF-like domain (3789–3828) and the second cluster of EGF-like repeats (4013–4181) are both present and are linked to the control of extracellular signaling and receptor engagement. FAT1 is anchored to the plasma membrane via the single-pass transmembrane domain. Through interactions with cytoskeletal and Hippo pathway elements, including scaffolding proteins that control YAP activity, the intracellular domain (4203–4588) controls downstream signaling. A representative mutation site commonly found in cancer genomic investigations is indicated by the red star

promoter region [6].

Function of FAT1

Circular FAT1(circFAT1) is a noncoding RNA with a cyclic structure. It was first identified in osteosarcoma in 2018 [7]. It originates from back-splicing of exon 2 of the *FAT1* gene and head-to-tail binding. CircFAT1 has a dual function; it either inhibit or initiate tumor progression in cancer by sponging miRNAs and subdues their downstream pathways [8, 9]. In some cancers such as ESCC, downregulation of circFAT1expression by siRNA activates ESCC cell migration and invasion ability, but not proliferation. Moreover, the expression of miR-548 g was amplified, which promoted ESCC cell migration and invasion [10].

However, in HNSCC circFAT1 is considered one of the 6th highly expressed circRNAs and is associated with shorter overall survival (OS) [8]. CircFAT1 favors HNSCC progression by binding with STAT3 and inhibiting it signaling pathway (35). The knockdown of circ FAT1promotes the efficacy of PD1 immunotherapy by enhancing CD8+ infiltration into tumor tissues. In addition, circFAT1 expression is upregulated in HCC tissues and cells and is associated with TNM stage and tumor size [11]. Depletion of circFAT1 inhibits the proliferation and invasion of HCC cells in vitro and tumorigenesis in vivo.

ONCOGENIC PATHWAYS

FAT1 as a tumor suppressor gene

FAT1 is downregulated in different types of cancers and plays a crucial role in cell activities such as cell proliferation and migration; it has been concluded to be a tumor suppressor [12]. Tumor initiation and progression have been demonstrated to occur in cancer initiating cells, which are also called stem-like cells. Moreover, Fat1-cKO cells, presented stemness as an increased number of spheroids in Fat1-knockout cells compared with those in FAT1 wild-type cells [12]. However, overexpression of wild-type FAT1 decreased the expression of stem-like cell markers and suppressed the formation of spheroids in non-small cell lung cancer (NSCLC) cells [13]. FAT1 may inhibit tumor-initiating ability in NSCLCs by promoting Yes-associated protein 1 (YAP1) nuclear-cytoplasmic translocation [13].

FAT1 as a possible cancer type-specific metastatic suppressor or promoter

Moreover, FAT1 suppresses tumor initiation but also suppresses metastasis. Inactivation of FAT1 causes epithelial-mesenchymal transition (EMT) through many signaling pathways [12, 14-17]. High levels of FAT1 expression inhibit cell proliferation, colony formation and cell migration and invasion. Low expression of FAT1 results in a decrease in E-cadherin expression along with increased N-cadherin, vimentin, and snail expression mediated by MAPK/ERK signaling, but high expression of FAT1 has the opposite trend [12].

Abnormal signal transduction of mutated FAT1

Owing to its numerous biological activities in terms of cell growth and cell–cell interactions, FAT1 is involved in the regulation of many signaling pathways; therefore, mutation of FAT1 causes the dysregulation of these signaling pathways which initiates carcinogenesis and cancer progression (Figure 2). Mutated FAT1 releases β-catenin from the proteasomal degradation complex, which enhances the nuclear translocation and transcriptional activity of β-catenin. Mutated FAT1 also releases YAP1 from the Hippo complex and activates it as a transcription factor. It also enhances HER3 activation and IRS1 expression, which may contribute to the activation of multiple RTK signaling pathways.

A potential link between YAP1 and ERBB signaling may be due to an autocrine loop through the ligand EGF and NRGs [18].

Wnt/β-catenin signaling pathways

The stimulation of the Wnt/β-catenin signaling pathway involves three steps: transducing Wnt signals

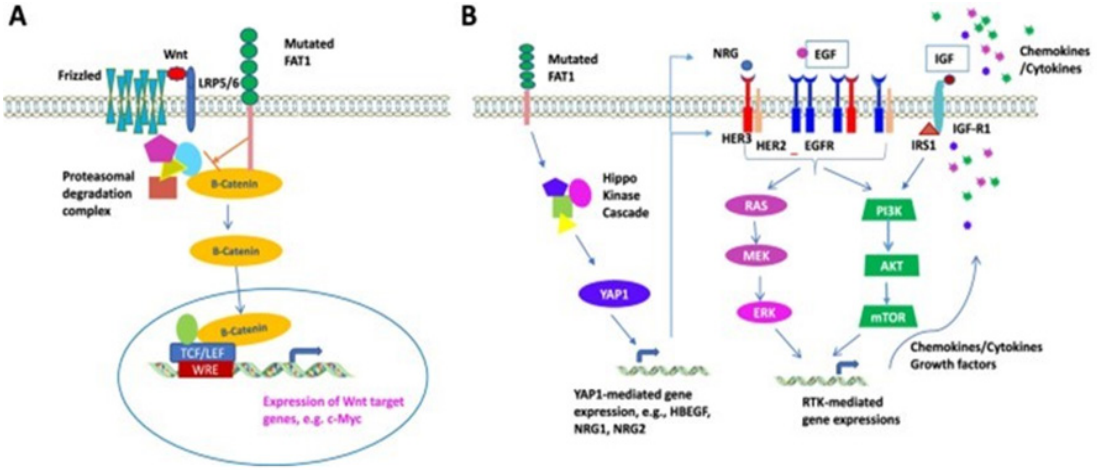

Figure 2.oncogenic regulatory pathways in many cancers. (A) Diagrammatic representation of how the Wnt/β-catenin pathway is affected by a mutation in FAT1. Under normal circumstances, the destruction complex targets β-catenin for proteasomal degradation. This control is upset by FAT1 loss or mutation, which encourages nuclear accumulation and β-catenin stability. By interacting with TCF/LEF transcription factors, nuclear β-catenin activates Wnt-responsive elements (WRE), which triggers the transcription of oncogenic target genes like c-Myc and other genes linked to proliferation. (B) Mutated FAT1 hinders the Hippo signaling pathway's activation, which lowers the activity of the Hippo kinase cascade and increases YAP1's nuclear localization (YAP1). Receptor tyrosine kinases (RTKs) like EGFR, HER2, HER3, and IGF-1R are stimulated by growth-promoting ligands like HBEGF, NRG1, and NRG2, which are transcriptionally induced by activated YAP1. Tumor cell proliferation, survival, and cytokine/chemokine production are all improved by this activation, which sets off downstream RAS–MEK–ERK and PI3K–AKT–mTOR signaling pathways.

at the membrane, stabilizing β-catenin in the cytoplasm, and activating Wnt/β-catenin target genes in the nucleus. The FAT1 protein promotes Wnt signaling by initiating β-catenin activity. Inhibition of FAT1 causes a decrease in plasma membrane β-catenin staining and a very high increase in nuclear β-catenin translocation [19]. Therefore, inactivated *FAT1* expression can affect gene expression, which is initiated by the Wnt/β-catenin pathways.

Hippo/YAP1 activation

The Hippo/YAP1 pathway is one of the crucial oncogenic regulatory pathways in many cancers including HNSCC [20]. FAT1 is considered a type of cell surface modulator that is involved in the regulation of YAP1 activity [21]. Wild-type FAT1 assembles into a multimeric Hippo signaling complex, which is responsible for activating core Hippo kinases by TAOKs and finally YAP1 phosphorylation, but phosphorylated YAP1 becomes inactive. When FAT1 is mutated, YAP1 is not restrained by phosphorylation. However, it then acts as an oncogene in HNSCC. Therefore, targeting YAP1 may serve as a therapeutic option for cancers involving genomic alterations in *FAT1* tumor suppressor genes. FAT1 and PTPN14 control malignant progression and chemotherapy resistance through the Hippo/YAP1 signaling pathway [22]. Signaling, which is mostly activated by FAT1 mutation [21], can activate EGFR family members via enhancement of their ligands in ovarian cancer [23], which indicates a potential link between YAP1 and EGFR signaling. The YAP1/TAZ/TEAD transcriptional complex involves BRD4 to promote an active chromatin state and controls multiple oncogenic transcriptional programs in HNSCC [24].

EGFR family/MAPK/ERK signaling pathways

There is a significant increase in the level of p-ERK1/2 when FAT1is inhibited whiles high expression of FAT1 decreases p-ERK1/2 levels [16]. Moreover, knockout of FAT1 in HNSCC cell lines significantly reduce p-ERK, possibly as a result of EGFR inhibition [25]. HER3 belong to the EGFR family and therefore has a high affinity for binding to the growth factors neuregulin, and HER3. pY1289 is activated after the activation of EGFR family members [26, 27]. Moreover, IRS1 which is a regulator of IGF-1R, is also upregulated in FAT1 mutated HNSCC [28]. HER3 and IGF-R1 signals combine to activate ERK/MAPK, PI3K/AKT, and RAS/RAF pathways, and these pathways then initiate cell proliferation/survival, protein synthesis, and the cell cycle through CMYC [29, 30]. HER2_pY1248 [27] and RET_pY905 [31] are receptors that are upregulated via the activation of signaling molecules such as SRC_pY527 [32], SHC_pY317 [33].

Interaction between FAT1 and actin cytoskeletal dynamics

Actin dynamics is important in governing cell migration and cell–cell interactions. The FAT1 cytoplasmic domain uses some products of actin, such as Ena/VASP and Homer1/3 proteins, which control the actin polymerization complex [34, 35]. The inhibition of FAT1 results in the decreased uptake of endogenous VASP to the leading edge of the cell and suppresses of lamellipodial dynamics, inhibits polarization, and controls cell migration [36]. Actin-mediated cellular cytoskeletal dynamics have been reported to be associated with cancer cell progression and metastasis [37]. Moreover, inhibition of FAT1 may initiate cancer progression and metastasis via interaction with Ena/VASP and Homer-mediated cellular cytoskeletal dynamics [38].

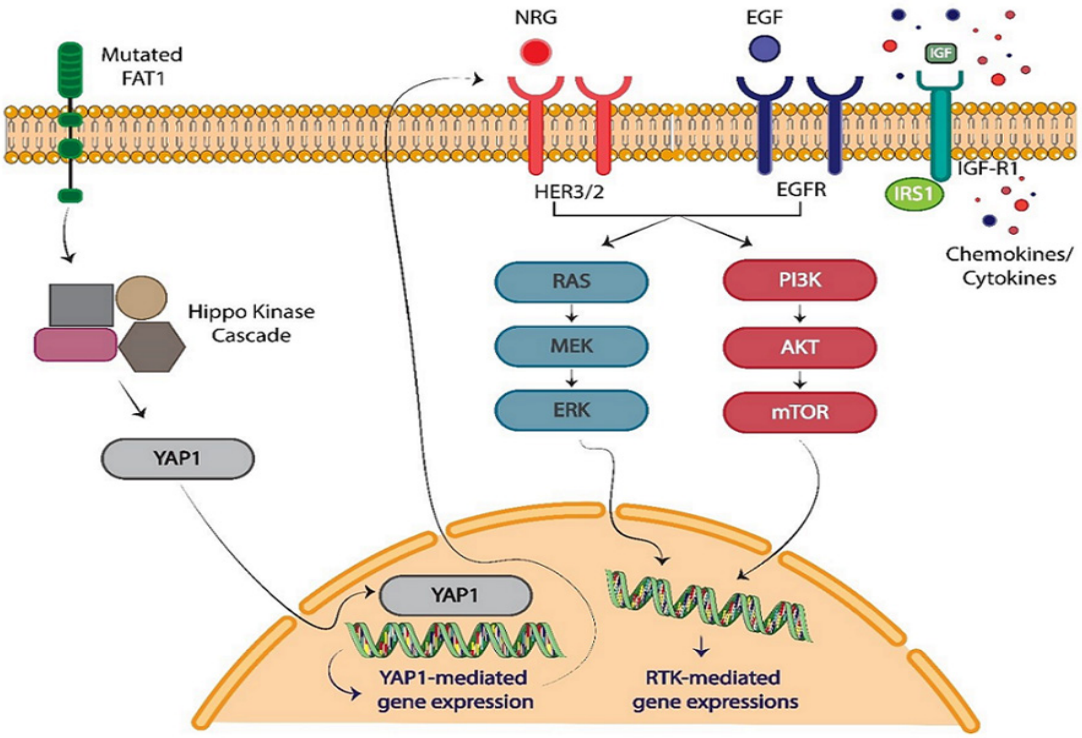

Figure 3. YAP1's Phosphorylation is Decreased and Its Nuclear Translocation is Increased when FAT Atypical cadherin 1 (FAT1) is mutated or lost, which hinders the Hippo kinase cascade's activation. YAP-dependent transcriptional pathways that drive tumor growth, survival, and proliferation are supported by nuclear YAP1. Simultaneously, downstream RAS–MEK–ERK and PI3K–AKT–mTOR pathways are stimulated by activation of receptor tyrosine kinases (RTKs), such as HER3/2 and EGFR in response to neuregulin (NRG) and epidermal growth factor (EGF), as well as IGF-1R signaling via IRS1. To improve RTK-mediated gene expression, these signaling cascades come together at the nucleus. YAP1 signaling and RTK pathway crosstalk increases oncogenic transcriptional outputs, which supports the proliferation, survival, and resistance to treatment of cancer cells.

Cancer related proteins affected by FAT1

Some regulators, such as *TP53* and CMYC, are considered to be potentially activated transcription factors and cell surface molecules. In a hypoxic environment, depletion of endogenous FAT1 can reduce the expression of HIF1a and its downstream target genes such as *CA9*, *GLUT1, VEGFA, MCT4, HK2, BNIP3* and *REDD1*. However, a significant reduction in invasiveness was observed in GBM cells [39]. Synergistic effects of FAT1 and CASP8 inactivation on the migration and colony formation of oral cancer cell lines have been reported [40], since both are usually mutated in oral cancers [41].

Hippo pathway and YAP signaling

The Hippo pathway and YAP signaling pathway control cell growth and organ size, and were discovered from the molecular and phenotypical characterization of the Hippo gene in Drosophila melanogaster [42]. The multimeric core complex of the Hippo pathway coordinates signaling from different upstream cues to control the activity of a downstream effector nuclear transcriptional module [42]. The Hippo pathway is usually active (Hippo ON) during cell growth restraining interaction in cells. Moreover, the serine/threonine kinases that make up the Hippo upstream core complex phosphorylate and cause the downstream transcriptional effectors in the cytosol. In contrast, in the absence of cell-to-cell interactions, such as normal tissue repair and renewal or embryo development, the mechanisms blocking gene transcription are usually switched off. This results in the activation of genes involved in cell proliferation and survival.

Schematic representation summarizing the main extrinsic (cell–cell contact and growth factor signals that regulate the Hippo-YAP Yes-associated protein pathway (Figure 3). The Hippo-YAP pathway initiates acellular switch. Cell-to-cell interactions stimulate the activation of the MST/LATS. Therefore, activated LATS phosphorylates YAP, which is then switched to ubiquitin-mediated proteasomal degradation or to cytosolic sequestration by binding to 14-3-3 protein, thereby preventing its nuclear translocation and switching off the expression of its target genes. When there is no cell-to-cell interaction, or in the presence of growth signals, the parameters of the Hippo core complex are inhibited. Non-phosphorylated YAP can move from the nucleus to the cytosol and bind to TEAD family transcription factors to initiate the expression of genes that promote cell proliferation, survival and migration [20].

Various parameters of the Hippo pathway

The Hippo pathway consists of two main elements. The first element is responsible for the integration of different stimuli that regulate the activity of a downstream effector element. The cytosolic multimeric signaling complex is formed by the serine and threonine kinases MST1 and

MST2 and LATS1 and LATS2 in MST1/2 and LAST1/2 interact with the adaptor proteins Salvador family WW domain containing protein 1 (SAV1) and(MOB kinase activator 1) MOB1, respectively [43, 44]. The Drosophila Hippo ortholog MST1/2 phosphorylates and activates LATS1/2, which also phosphorylates the transcriptional coactivator YAP and its dimerizing partner TAZ as a result of the active Hippo pathway. YAP1 in humans has two isoforms, namely, YAP1-1 and YAP1-2. TAZ is a transcriptional coactivator with a PDZ binding domain, also known as WWTR1, WW domain containing transcription regulator 1 [45, 46]. YAP1-1, YAP1-2, and TAZ have the same structure with similar functions. Moreover, YAP consists of sites that are usually phosphorylated by c-Abl/Scr/Yes and by JNK kinases, and also methylated by Set7 histone methyltransferases, which are absent in TAZ [47, 48].

YAP Signaling

The phosphorylation of YAP and TAZ by the LATS1/2 kinases of the Hippo pathway core complex promotes the interaction of YAP/TAZ with 14-3-3 proteins and their presence in the cytosol, or the ubiquitination and degradation YAP/TAZ [49, 50]. All these mechanisms cause YAP/TAZ nuclear inhibition, which prevents the transcription of target genes. The primary targets of this pathway genes-involve in cell adhesion and epithelial to mesenchymal transition (EMT), progression, cell cycle regulation, survival and stemness [51]. The largest YAP/TAZ-regulated gene transcription signature was accomplished via oral squamous cell carcinoma (OSCC) cell lines [51]. This signature revealed that, at least in this tumor type, YAP has a more prominent transcriptional role than TAZ. Moreover, YAP canonical targets such as connective tissue growth factor(CTGF) and cysteine-rich angiogenic inducer 61 (CYR61) do not significantly changes in terms of expression with respect to tumor grade [51].

Below are gene whose expression is controlled by YAP and TAZ in oral squamous cell carcinoma (OSCC) [51] and are involved in various signaling pathways which are important to head and neck squamous cell carcinoma (HNSCC) progression. When the activities of MST1/2-LATS1/2 are inhibited, YAP and TAZ are normally translocated to the nucleus, where they associate with DNA-binding transcription factors to control gene expression, because they cannot bind to DNA [52]. The major transcription factors that initiate YAP/TAZ activity are those that belong to the TEA domain transcription factor (TEAD) family, which consists of TEAD1 to TEAD4. YAP function can be inhibited when TEADs are absent [53]. YAP and TAZ can also bind to transcription factors such as activator protein 1 (AP-1), the internal domain (ICD) of ERBB4 (erb-b2 receptor tyrosine kinase 4), SMADS, transcription factors of the RUNX family and p73. The association between YAP-TAZ-TEAD andAP-1 activations is involved in S-phase [54]. Moreover, the ICD of ERBB4 binds with YAP and TEAD to initiate its activities in breast cancer cell lines [55]. The association of the coactivator

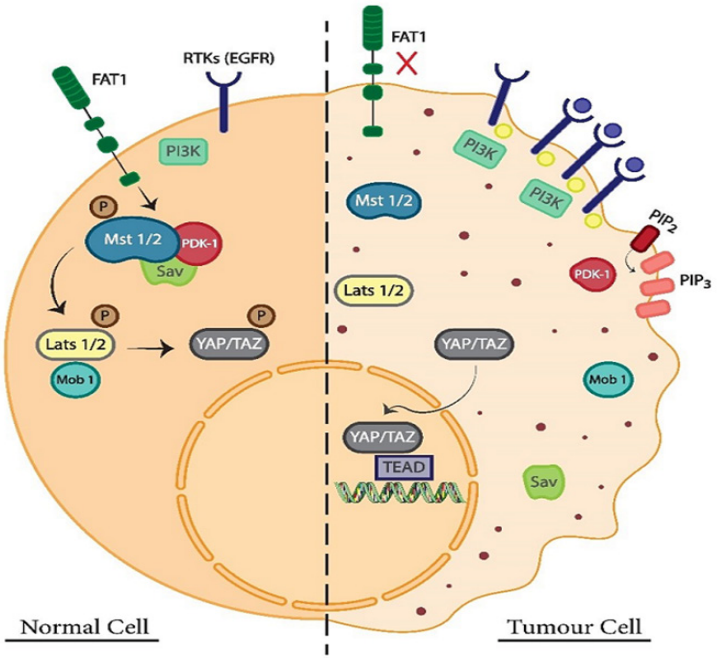

Figure 4. The Signaling Events in a Normal Cell, where FAT1 Acts as a Tumor Suppressor, are Depicted in the Left Panel. The Hippo kinase cascade, which includes Mst1/2, Sav, Mob1, and Lats1/2, is assembled and activated by FAT1. YAP/TAZ are phosphorylated by activated Lats1/2, which causes their cytoplasmic retention and destruction. This stops TEAD-mediated transcription of pro-proliferative and anti-apoptotic genes and stops YAP/TAZ nuclear translocation. Additionally, normal cellular homeostasis is supported by the maintenance of controlled PI3K–PDK1 signaling.A tumor cell with missing or inactivated FAT1 is shown in the right panel. Hippo pathway activation is hampered by FAT1 disruption, which lowers the activity of Mst1/2 and Lats1/2 kinases. Consequently, YAP/TAZ stay unphosphorylated and go into the nucleus, where they bind TEAD transcription factors and activate genes related to tumor growth, survival, and proliferation. Oncogenic signaling pathways are further promoted by increased PIP3 production brought on by enhanced PI3K–PDK1 signaling.

bromodomain-containing protein (BRD4) with that of YAP-TAZ-TEAD1 favors the transcription of genes that cause tumorigenesis and therefore opens the way for new therapeutic strategies targeting BRD proteins to deactivate YAP activity in tumors [56]. The binding of YAP/TAZ to SMADS combines the Hippo and transforming growth factor-β (TGF-β) pathways, hence linking activities such as cell density corresponding to TGF-β [57]. In tumors, such as gastric and breast cancer, RUNX factors have tumor suppressor activity via the generation of RUNX-YAP-TEAD complexes that control the transcription of YAP-TEAD target genes to prevent the oncogenic activities of YAP [58]. With DNA-damaging drugs, YAP normally translocates to the nucleus and associates with p73, thereby increasing its stabilization, enhancing its acetylation by p300. This results in the transcription of the p73 proapoptotic target genes *p53AIP1* and *BAX* [59]. In addition, in HNSCC cell lines, the overexpression of ΔNp63 inhibits YAP expression and the expression of apoptotic genes to support cell survival, whereas the YAP silencing promotes proliferation, survival, migration, and resistance to cisplatin [60].

Stimulating and Inhibition of the Hippo Pathway

The signaling pathway that involves the activation of the Hippo pathway interacts with neighboring cells. Moreover, cells respond to the nature of extracellular matrix and the extracellular growth factors. Multimeric aggregates located in different cell membranes are involved in maintaining adherence, tight junctions and cell polarity. The regulation of apical-basolateral polarity is crucial in epithelial cells thus, controls important characteristics, such as stemness, differentiation and cell function. The absence of cell polarity leads to dysplasia and finally to EMT, which is considered a hallmark of cancer [61]. The cadherin-catenin complex at the junctions and the PKC-PAR complex at thigh junctions [57, 62], normally work together as scaffolds that use the kinases of the multimeric core aggregates of the Hippo signaling pathway, thereby increasing the activation of MST1/2 and LATS1/2 and inactivation of YAP/TAZ. In addition, α-catenin at its junctions prevents the formation of phospho-YAP/14-3-3 complexes and subsequently inhibits YAP activation (Figure 3).

Through regulation of the Hippo-YAP pathway, target cells and the extracellular matrix (ECM) can respond and adapt to changes such as density and polarity. However, the properties of the ECM may differ in physiological processes and diseases, such as changes in tissue remodeling and regeneration, inflammation, fibrosis and cancer. YAP/TAZ transcriptional activity can be modulated in different cell types, including human mammary epithelial cells [63]. The YAP target genes include genes encoding ECM components and ECM-modifying enzymes that alter the ECM composition [62]. When ECM activities are altered, carcinogens interact with fibroblasts, thereby favoring the deposition of thick and rigid collagen fibers that promote the growth of cancer cells [64]. Moreover, intracellular cell shape and tension impact cytoskeleton contractility and control the activity of YAP/TAZ via Rho GTPase-Rho interactions with kinases (ROCK) without the presence of Hippo core kinases [65].

The Hippo-YAP pathway interacts with other pathways through cross-talk with signals from the TGF-β, Wnt and growth factor pathways and via metabolism. YAP/TAZ interconnect with the TGF-β pathway so that reactions to TGF-β can be regulated by cell density. These activities transmit cell density information by initiating YAP/TAZ cytoplasmic retention. However, TGF-β signaling is inhibited because TAZ functions as a SMAD nuclear retention factor. The loss of cell density and polarity can disrupt of the YAP/TAZ nuclear translocation, thereby promoting TGF-β signaling and enhancing ability of the cells to undergo TGF-β-mediated EMT [57]. Epidermal growth factor (EGF) and Wnt ligands (Wnts) prevent the effects of cell-contact growth inhibition and rather initiate YAP/TAZ transcriptional activity [66]. The activation of the PI3K-PDK1 axis is a result of EGF binding to its receptor and of lysophosphatidic acid (LPA) binding to G protein-coupled receptors (GPCRs). When PDK1 interacts with MST and LATS kinases, LATS1/2 is activated and therefore translocated to the cytoplasmic membrane causing the dissociation of the complex to cause the loss of LATS1/2 activation and the accumulation of YAP the nucleus [67]. When Wnts bind to GPCRs YAP is activated via the canonical Wnt pathway, which involves the inhibition of axin/adenomatous polyposis coli/glycogen synthase kinase 3 (Axin/APC/GSK3) destruction complex and the release of β-catenin and YAP, thus resulting in the transcription of their target genes [66] (Figure 4). Through this mechanism, the Hippo pathway can deactivate Wnt signaling. Cytosolic YAP/TAZ, together with disheveled segment polarity protein (DVL) can control the stability of β-catenin in the cytosol as a result of the inhibition of Wnt signaling [68], thus high levels of cytosolic YAP inhibit intestinal crypt proliferation [69]. YAP is required to favor APC-deficient adenomas [70] and tumorigenesis viaβ-catenin which favors cancer progression via the formation of YAP-β-catenin-TBX5 transcriptional complexes [71]. Therefore, the interconnection between Hippo and Wnt pathways may depend on the cell type, cell context and subcellular location. The intrinsic signals such as energy stress, glucose metabolism, aerobic glycolysis and the mevalonate pathway can control YAP activity [72-74].

The Hippo-YAP Signalling Pathway in HNSCC

The signaling pathway controlling cell growth, which interacts with to other cell activities such as cell polarity, adhesion, cytoskeleton dynamics, cell survival factor signaling and metabolism, is uncontrolled during cancer initiation, progression and metastasis. Other components of the Hippo pathway are considered oncogenes (YAP, TEADs) or tumor suppressors (LATS1/2) [75]. In addition, many of these signals controlling Hippo-YAP activity favor cancer pathways [75].Compared with alterations in its components, YAP/TAZ-dependent gene expression is not well controlled in human cancer as YAP/TAZ can stimulate the expression of specific genes to which cancer cells are addicted by binding to chromatin readers [76]. Additionally, the YAP/TAZ signaling is susceptible to normal homeostasis in adult tissues [77-79] thus, this

pathway is considered to be a therapeutic target in cancer.

Approximately 10 % of alterations in the Hippo pathway in human cancer have been reported [75], but this figure is greater than 90% in low-grade glioblastoma, approximately 50% in microsatellite instability-DNA polymerase epsilon (MSI-POLE) subtypes in colorectal, stomach and endometrial tumors, and 42% in HPV negative HNSCC [75]. HNSCC affects the head and neck regions, and because of the different locations of the cancer, the first site where the tumor arises could influence the characteristics of the tumor, including its genetic features. However, there is a paucity of data showing an association between alterations in Hippo pathway genes and different locations in HNSCC. Two upregulated pathways that are mostly altered in HNSCC are FAT1 and PIK3CA. The inhibition of FAT1 as a result of deletion, truncating mutations, and the activation of PIK3CA are associated with YAP-dependent transcriptional activation in HNSCC [80]. However, the particular molecular mechanisms that contribute to tumor development in relation to FAT1 functional loss and PIK3CA overexpression are not fully understood (Figure 4) [21]. FAT1 interacts with MST1, which initiates its phosphorylation and the assembly of the Hippo kinase core complex results tin the phosphorylation of LATS1/2 and YAP in HNSCC cell lines [21]. High expression of PIK3CA is associated with poor outcomes in HPV negative HNSCC, indicating the nuclear localization of YAP and a YAP-activation transcriptional signature [80]. The PI3K-PDK1 pathway is interconnected with signals from fibronectin, LPA, GPCR receptors and EGFR [81]. However, although nuclear YAP localization has been observed in oropharyngeal HPV positive tumors [82], Hippo pathway alterations and that of FAT1 inactivation or YAP amplification are not commonly seen in HPV positive HNSCC [75] (Figure 3). PIK3CA alterations are commonly identified genetic events in HPV positive tumors [83], and it has been shown that the HPV E6 oncoprotein can destroy the Hippo core complex scaffolding element Scribble [84].

Schematic representation showing the potential molecular mechanisms involved in tumor development in the context of FAT1 (FAT atypical cadherin 1) functional loss, EGFR (epidermal growth factor receptor) amplification or PIK3CA (phosphatidylinositide 3-kinase catalytic subunit alpha) overexpression in head and neck squamous cell carcinomas (HNSCCs). Note that PIK3CA codes for the catalytic subunit of PI3K (phosphatidylinositide 3-kinase). In nontumor cells, in the presence of low levels of EGFR and normal PIK3CA expression, PDK1 (phosphoinositide-dependent kinase 1) forms a complex with the Hippo signaling core complex, promoting YAP phosphorylation. Similarly, FAT1 acts as a scaffold for Hippo kinases, thus promoting their activation. In a tumor cell, the absence of FAT1 or the presence of high levels of EGFR and increased PI3K activity, which recruits PDK1 to the cell membrane, dismantles the Hippo core complex leading to YAP dephosphorylation and its translocation to the nucleus. RTKs: receptor tyrosine kinases.

Under normal physiological conditions, the levels of YAP and TAZ in the oral epithelium is low apart from those in basal layer cells, indicating that nuclear YAP and TAZ staining can be observed as shown in Figure 4. In case of hyperplasia and dysplasia, cells remove nuclear YAP extend beyond the basal cell population and are common in regions of critical dysplasia [51]. There are currently no study indicating YAP and TAZ are significantly mutated, amplified and overexpressed in OSCC. YAP and TAZ expression are not correlated with tumor stage or grade [51]. These findings indicates that alterations in YAP/TAZ upstream regulators such as FAT1 and PIK3CA in HNSCC [80] occurs during the progression of HNSCC tumor which results in the activation of these two co-transcriptional factors and target genes. The expression levels of both YAP and TAZ in OSCC cell lines indicate that YAP is more important than TAZ in the regulation of transcription, more especially in OSCC [51]. TAZ overexpression has been associated with poor outcomes in patients and aggressive tumor grade or stage in OSCC [85]. Moreover, YAP/TAZ transcriptional targets in OSCC [51] indicate that increased expression of TEAD4 is associated with increased tumor grade and stage in the TCGA -dataset of HNSCC [51]. In addition, TEADs can stimulate YAP/TAZ nuclear retention [86] thereby promoting YAP/TAZ-TEAD4-mediated gene transcription in these tumors. In HNSCCs, YAP amplification and overexpression correlate with poor prognosis in different HNSCC cohorts [87]. Additionally, the YAP-inactivated subgroup is associated with an HPV positive status, similar to the absence of YAP amplification in HPV positive HNSCC [75].

Immune Regulation

FAT1 in immune regulation

Mutations in *FAT1* were associated with high infiltration of activated dendritic cells. Mutations of FAT2/3/4 were associated with high infiltration of CD8+T-cells, M1 macrophages, activated memory CD4+ T-cells and helper follicular T-cells. Mutation of FAT1/2/3 was also correlated with progression-free survival in an immune checkpoint inhibitor (ICI)-treated NSCLC cohort [88]. High FAT1 mutation rate was associated with high tumor mutational burden (TMB), which can be used to predict patients' response to ICIs in NSCLC [88]. Similarly, patients with melanoma and NSCLC harboring FAT1 mutations have been reported to have favorable survival outcomes from ICI therapy [18]. High TMB was associated with increased infiltration of immune-response cells and decreased infiltration of immune-suppressive cells, interferons and cell cycle-related pathways in patients with FAT1 mutations (98).

Therapeutic Implications

FAT1 is a mutated protein in cancer and is therefore considered a diagnostic and prognostic biomarker. FAT1 is highly expressed in acute lymphoblastic leukemia, breast cancer [89], NSCLC [90], gastric cancer [91]. There is an association between FAT1 mutation and overexpression in the prognosis of different cancers, such as HNSCC and worse disease-free survival (DFS) [92]. Five-year survival and recurrence-free survival rates are lower in the FAT1-HR subgroup than in FAT1-LR subgroup

[93]. In addition, the oropharyngeal squamous cell carcinomas (OPSCCs) were mostly HPV (+). However, FAT1 mutation occurs predominantly in HPV(-) SCC. Additionally, metachronous recurrent OPSCCs have been seen to have similar genomic characteristics to HPV-unrelated HNSCCs, including FAT1 mutations [94]. However, there are still FAT1 mutations in recurrent HNSCC even when HPV is negative. HNSCC patients with FAT1 mutations have a shorter progression-free survival than those with wild-type FAT1 [25]. Therefore, FAT1 represents a promising prognostic biomarker.

Abnormal expression of FAT1 has also been associated with sensitivity to cancer treatment. [95]. The recruitment of a stop-gain mutation in FAT1 indicated a tendency towards increased sensitivity to the mTOR inhibitor, temsirolimus [12]. However, compared to the wild type, FAT1-knockout tumor cells were more sensitive to the SRC inhibitor dasatinib, the SRC/Bcr-Abl inhibitor saracatinib, and the CAMK2 inhibitor KN93. Genomic analysis of 348 estrogen receptor-positive breast cancer patients treated with a CDK4/6 inhibitor revealed that aloss-of-function mutation of FAT1 led to resistance to the CDK4/6 inhibitor via the Hippo/YAP1 signaling pathway [96]. A clinical trial used the HER3 inhibitor CDX-3379 and the EGFR inhibitor cetuximab in metastatic, HPV-negative, cetuximab-resistant HNSCC [97]. According to recent study, FAT1 downregulation in ESCC initiates stemness and reduces patient sensitivity to cisplatin [98]. They reported that, knockdown of FAT1 could stimulate multidrug resistant protein ABCC3 via FAT1-mediated nuclear translocation of β-catenin. The effect of FAT1 on drug sensitivity is related to aggressive behaviors, such as the stemness and EMT status of cancer cells. Some surface receptors and signaling molecules, such as HER3 phosphorylation, are associated with FAT1 mutation, and are considered to suppress the oncogenic pathway initiated by FAT [99]. In gastric cancer, FAT is overexpressed but the use verteporfin can suppress FAT1 expression which results in decreased migration and invasion of gastric cancer cells [99]. Genomic alterations in the Hippo pathway and persistent YAP/TAZ activation in HNSCC [99]. Because the occurrence of FAT1 is high in this disease, inhibiting this pathway may result in multimodal precision therapies for HNSCC. Proteomic and drug-screening studies across multiple cancer models confirmed that FAT1 mutated HNSCC had increased sensitivity to BRD4 inhibition by JQ1 also which has been used to block YAP1 signaling [24]. Therapeutic peptide have also been shown to inhibit the FAT1-associated protein complex [100-102].

Author Contribution Statement

Roland Osei Saahene conceptualized the study, performed the literature review, and contributed to manuscript writing and editing. Specifically, Precious Barnes contributed to data curation and literature review, and critically revised the manuscript. Du-Bois Asante was involved in manuscript drafting, figure preparation, and critical analysis of the signaling pathways discussed. Sylvester Acquah Famieh contributed to manuscript organization, proofreading, and final review. All the authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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