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Fat1 Mutation and Its Significance in Head and Neck Squamous Cell Carcinoma (Oscc)-A Review

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ABSTRACT

The *FAT* gene family plays a notable role in various biological processes in vertebrates. They function as a tumor suppressor, maintaining planar cell polarity essential for the proper orientation of cells within a tissue. As with many solid tumors, OSCC also has an array of genetic alterations. *FAT1* has garnered significant attention among the *FAT* genes (*FAT1*, *FAT2, FAT3, and FAT4*) due to its prominent role in cancer progression and its high mutation rate in various cancers, particularly among the head and neck squamous cell carcinoma (HNSCC). The down-regulation of FAT1 has a direct influence on the clinical outcome of patients with OSCC. The FAT1 mutation has shown its role in tumorigenesis and in metastasis in OSCC thus, making it an essential diagnostic biomarker and therapeutic target in the treatment of OSCC.

Keywords: *FAT1, FAT1 gene mutation, OSCC, HNSCC, biomarker*

1. INTRODUCTION

Oral squamous cell carcinoma (OSCC), a subtype of head and neck squamous cell carcinoma, remains a major reason for morbidity and mortality. Based on the stage of diagnosis and anatomic location, the treatment strategy includes surgery, radiotherapy, or both combined (1). As with many solid tumors, OSCC also has an array of genetic alterations. FAT1 has garnered significant attention among the *FAT* genes (*FAT1, FAT2, FAT3*, and *FAT4*) due to its prominent role in cancer progression and its high mutation rate in various cancers, particularly among the head and neck squamous cell carcinoma (HNSCC) where it ranks second the most frequent mutated gene (1, 2). The role of *FAT1* is highly discussed, whether being

a tumor suppressor or a tumor promoter. This review summarizes the role of FAT1, with the objective of promoting its significance as a biomarker and a potential therapeutic target for the management of OSCC.

Physiological role of normal FAT1

The adhesion between the cells is highly significant in the morphogenesis, growth and development of multicellular organisms. The aberrant internal environment of the cell highly influences the cadherins in pathological conditions such as autoimmune disease, kidney disease, and malignancy. Cadherins are calcium-dependent cell adhesion proteins. They not only act as linker proteins but are also involved in signaling pathways. The cadherins comprise a large family of cell adhesion molecules, which are subdivided into several subfamilies with their own unique functions. It includes classical cadherins, desmosomal cadherins, protocadherins, Flamingo/Celsr, Dachsous and FAT cadherins. Classic cadherins have five – cadherin repeated domains and a highly conserved cytoplasmic region to which the catenin system binds and links to the actin cytoskeleton. The function of classical cadherins is well established. It is essential for cell-cell adhesion by organizing the adherens junction. The Desmosomal cadherins, which also have five cadherin repeats, link with the intermediate filament through plakoglobin and desmoplakin. Protocadherins have 5-27 cadherin repeats with divergent cytoplasmic sequences. The CDH23 protocadherin is significant in stereocilia organization and PAPC protocadherin in convergence and extension movements during gastrulation.

FAT cadherin proteins are the largest most prominent cadherin superfamily. It was first described in Drosophila in the 1920s. It was discovered due to its lethal mutation in Drosophila. FAT and FAT–like are the two FAT cadherins in Drosophila. Hyperplastic overgrowth of the imaginal disc of the Drosophila larvae, and also the involvement of its wing, leg, eye, antenna, glands, and genital imaginal disc, led to the knowledge of its role as a tumor suppressor protein. Peng et al. stated the mutation of FAT cadherins influenced an 'epithelial overgrowth phenotype in Drosophila. An enlarged wing imaginal disc displaying extra folds and outgrowth of the proximal wing was observed in the case of strong FAT cadherins mutation. It is hypothesized that FAT can influence the localization and expression levels of the transcription factors involved in the Hippo signaling pathway, Yorkie, Warts, and Expanded Drosophila exhibiting overgrowth phenotype. In addition the FAT plays its role in regulating planar cell polarity (PCP). PCP is observed in the wing hairs and ommatidia of Drosophila. The FAT mutant Drosophila, the ommatidia, exhibit reversed dorsal-ventral polarity.The second FAT cadherin member, FAT-like, influences the morphogenesis and also the development of tubular structures of ectodermal origin. By using RNA interference knocking down of FAT-like cadherins results in abnormal development of renal tubular structure, lack of formation or small deletion of trachea, gastric glands and salivary glands. Thus the loss of FAT influences the overgrowth phenotype, and FAT-like influences the formation of tubular structures in Drosophila, providing an understanding and urge for the study of FAT cadherins in vertebrates (3).

The vertebrate FAT cadherin proteins are homologous to the Drosophila *FAT* proteins. The *FAT* gene family comprises *of FAT1, FAT2, FAT3* and *FAT4* genes. The *FAT* gene family does a notable role in various biological processes in vertebrates. The structure and function of the *FAT* family is highly conserved. *FAT1* and *FAT4* commonly have 34 EC domains, and FAT2 contains 32 EC repeats, and *FAT3* has 33 repeats. The arrangements in its number of laminin G motifs and EGFlike motifs render its function individually unique. The mammalian FAT might have acquired functional similarity to *FAT*s in Drosophila since its extracellular domains appear similar. It is found to be expressed in various tissues at embryogenic stages in proliferating epithelial tissues, skin and in the lung epithelium. It plays a role in cell proliferation and establishing planar cell polarity (3). The role of the *FAT* family was considered as a tumor suppressor; however, its role is yet to be explored. The extremely large size of mRNA transcript and encoded proteins render a challenge in understanding its function in vertebrates. Among the four, *FAT1* was highly focused due to its prominent mutation effects in acute lymphoblastic leukemia and hepatocellular carcinoma (3, 4).

The *FAT1* gene was identified from a human Tcell ALL (TALL) cell line in 1995. It is located on chromosome 4q3435 with 27 exons in humans. *FAT 1* is a type I transmembrane protein encoding 4588 amino acids, comprised of an extracellular 34 cadherin repeats,5 EGF-like repeats, and laminin G-like domains, which are followed by a transmembrane region, and an intracellular domain that contains PDZ binding motif. (Fig 1)(2, 3).

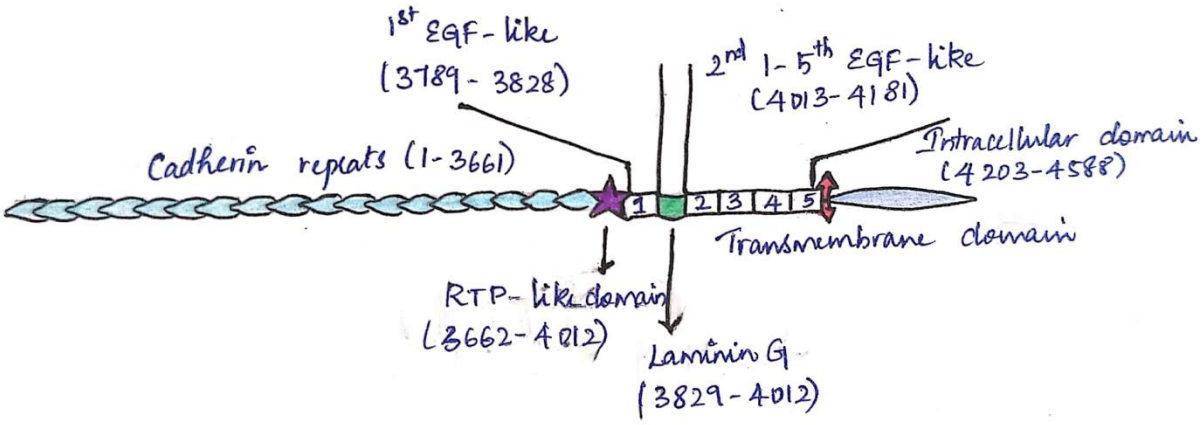

Fig: 1 Structure of *FAT1* protein

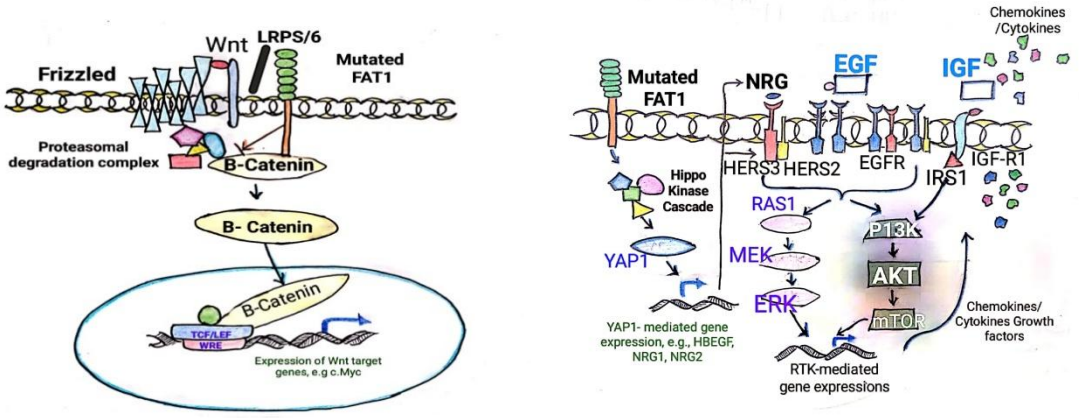

Fig2:*FAT1* mutation and its associated signaling pathways

It is found to be expressed in the proliferating epithelial tissue such as neuro epithelium, lung, kidney and skin basal layer (5). *FAT1* shows a restricted expression pattern with its peak in an embryonic stage, which diminishes at the adult stage. This pattern of expression is also observed in the cell lines. Tanoue and Takeichi have found the high expression of *FAT1* in PAM212 cells, a transformed keratinocyte cell line, while expression is low in MDCK cells, a kidney epithelial cell line, thus establishing its localization in the cell. Tanoue and Takeichi, in their detailed examination, reveal the localization of *FAT1* in filopodia tips, lamellipodial edges, and cell-cell contacts. *FAT1* localization is necessary for tight cell-cell contact and proper actin organization. *FAT1* is mainly localized at the basolateral region and at the lower levels at the apical junctions. *FAT1* also gets accumulated in the protrusions of the basal portions of the cells where convergence of actin fibers are found. In addition, low levels of expression were observed in the confluent cells.

The FAT1 highly influences the actin dynamics. The actin filaments are recruited to the junction sites and the formation of radial actin cable was observed at cell-cell contact in the early stages of PAM212 cell lines (5). In addition, the cytoplasmic tail of *FAT1* promotes the actin stress fiber formation in MDCK cell lines emphasizing the role of *FAT1* in actin dynamics. Knockdown of FAT1 results in loss of cell adhesion; however its effect cannot be ascribed only to the role of FAT1 since actin disorganization can also disturb classic cadherins(5).The localization of FAT1 at the lamellipodial edges also regulates the actin dynamics.FAT1-knockdown NRK-52E cells exhibit abnormal lamellipodial dynamics at the wound margins, resulting in delayed wound closure. In addition, it was also observed that cell-cell adhesions were not disturbed in NRK-52E cells, indicating *FAT1* seems to be a cell-specific-dependent action (5).

FAT 1 acts as a molecular “brake” in mitochondrial respiration and also regulates the proliferation and migration of vascular

smooth muscle cells in case of arterial injuries (2, 6, 7). Longyue L. Cao et al. observed the expression of FAT1 by the smooth muscle cells is induced by exposure to the growth factor and vascular injury. The full-length *FAT1* appears to be unlikely a direct regulator of mitochondrial function. It was observed from the previous studies that cleavage of FAT1 yields multiple smaller species, including *FAT1* intracellular domain bearing derivatives of ~85 and ~65 kDa26.However, the factors or conditions that induce *FAT1* processing and its translocation of C-terminal fragments need to be understood. The observations of Longyue L. Cao et al. found a relatively direct mechanism for sensing the extracellular milieu and relaying signals to mitochondria that control respiratory chain activity and other metabolic functions (7).

Studies also have shown that the intracellular region of *FAT1* interacts with the Enabled (Ena)/vasodilator-stimulated phosphoprotein (VASP), thereby regulating the actin-mediated cell migration. It is regulated by antagonizing capping proteins and or it increases the rate of separation of the branched junctions on actin cytoskeleton. The three members of the (Ena)/vasodilator-stimulated phosphoprotein (VASP) family includes Mena, VASP, and Ena-VASP, like in mammals. It has an N-terminal EVH1 domain, a proline–rich central domain, and a C-terminal EVH2 domain.*FAT1*found to have three potential binding sites to the EVH1 domain in its cytoplasmic domain.*FAT1* colocalizes with Ena/ VASP and controls early cell-cell contact sites by the formation of the junction actin cytoskeleton.*FAT1* knockdown in PAMP212 cells and in NRK-52E cells of the accumulation of VASP protein at the leading edges, establishing its role in actin dynamics. In addition the regulation of Ena/VASP is a unique function of *FAT1* (5,8).Further, the intracellular portion of *FAT1* shows direct interaction with the Scribble protein inhibits YAP 1-mediated cell proliferation (8, 9, 10). The Scribble is the scaffold proteins with multiple PDZ domains.It binds to the HTEV motif of the c-terminal domain of *FAT1*. Both act synergistically in the cytogenesis phenotype mediated through the inhibition of YAP1 signaling (4,10).

The role of Wnt/β-catenin signaling pathway is well established in embryogenesis as well in adult tissue homeostasis.This pathway involves three steps. Wnt signal transduction at the cell membrane, stabilization of β-catenin in the cytoplasm and activation of Wnt/β-catenin target gene in the nucleus. *FAT1* modulation is involved in the later two steps of this pathway (11). Under normal conditions, *FAT1* can bind to β-catenin, limiting its translocation to the nucleus. This interaction was confirmed by Hou et al., in their demonstration in rats. There is increased *FAT1* expression following carotid artery injury where the cytoplasmic tail of *FAT1* binds to β-catenin, preventing its translocation into the nucleus and transcription of the target gene. Cyclin D1 is a known target gene in this pathway, which regulates the G1 phase and G1/S phase transition in the cell cycle (12).

FAT1 protein acts as an upstream factor in regulating the Hippo signaling pathway. The Hippo signaling pathway, the Salvador (Sav)-Wts-Hippo pathway, is crucial for regulating organ size and tumorigenesis. The intracellular domain of FAT1 interacts with the core to the Hippo core kinase cascade via kinase Tao wherein Mst1/2 (ortholog of Drosophila Hippo) kinases and SAV1 form a complex to phosphorylate and activate LATS1/2. LATS1/2 kinases in turn phosphorylate and inhibit the transcription co-activators YAP and TAZ, two major downstream effectors of the Hippo pathway. Knockout of the *FAT1* causes YAP/TAZ not to get phosphorylated. YAP/TAZ translocates into the nucleus and interacts with TEAD1-4 and other transcription factors to induce the expression of genes that promote cell proliferation and inhibit apoptosis (13).

The MAPK/ERK signaling pathway is also involved in proliferation, cell differentiation and apoptosis (3).The abnormal activity of this pathway is observed in multiple myeloma, lung carcinoma and in Hepatocellular carcinoma.*FAT1* mutation results in increased MAPK activity by phosphorylation of ERK protein in HCC, while in esophageal squamous cell carcinoma, the proliferation of the cells occurs due to the loss of control of this pathway(14). The Knockout of *FAT1* significantly increased the levels of p-ERK1/2 while its exogenous expression controls the cell proliferation, migration and invasion, indicating the role of *FAT1* acts as a tumor suppressor(14).

FAT1 also influences epithelial mesenchyme transition (EMT), which is a cellular process that promotes the migration of cells, invasion and stemness of the cells. Hu et al. observe the association of *FAT1* to EMT in ESCC. Inhibition of *FAT1* decreases the expression of epithelial E-cadherin and increases stromal markers such as N-cadherin, vimentin, and snail, emphasizing FAT1 as a key regulator in EMT(14).*FAT1* influences EMT through the MAPK/ERK pathway. Treatment with U0126, an ERK1/2 phosphorylation inhibitor, reverses the changes in marker expression caused by *FAT1* inhibition, suggesting that *FAT1* is a key regulator of EMT and could be a potential target for cancer therapy(14).

Role of *FAT1* in embryonic development

FAT1's role in the development of human tissues is limited, yet it seems to be more prominent. In situ hybridization expresses the high levels of *FAT1* mRNA in the embryonic stem cells, fetal epithelium, and in kidney tissues. It is expressed throughout and also controls neuromuscular morphogenesis. *FAT1* expression is down regulated following the development of organs, and its expression is at low levels in adult tissues, understanding its peak role during organogenesis (14, 15).

Role of *FAT1* in hereditary disease

Mutation of *FAT1* is observed in 4q syndrome (facial deformity, cutaneous syndactyly, ocular abnormalities with or without nephropathy), Facio scapulo humeral muscular dystrophy and Bipolar affective disorder. The loss of *FAT1* function results in weak adhesion of epithelial cells,defective lumen formation in hormone-resistant nephritic syndrome, and

glomerulonephritis. It also impairs the adhesion between the epithelial cells, resulting in fissures and defects in neural tube closure (16). In Facio scapulo humeral muscular dystrophy, the *FAT1* expression is down regulated. This inactivation causes morphological alteration of the certain muscles of the face and the shoulders (17, 18). FAT1 is a susceptible gene in bipolar affective disorder. Single nucleotide polymorphism was identified in FAT1, likely to be involved in the etiology of BPAD (19)

FAT1 mutation and tumorigenesis in HNSCC.

FAT1, a frequently mutated gene in HNSCC, stands second, followed by TP53. *FAT 1* gene alteration rate was 29.8%(6). Nakaya et al. observed homozygous deletion in 23% of Oral cancer cell lines and in 80% of primary Oral cancer cases. The expression levels of FAT1 mRNA is also decreased in oral cancer cell lines because of homozygous deletion and or otherwise promoter CpG hypermethylation(4,20). In another study on HNSCC cases, about 29% of patients harbor *FAT1* mutation, which is a nonsense and missense mutation that results in decreased levels of expression or loss of *FAT1* mRNA and its protein (21,22). The migration and invasiveness of HNSCC cells were significantly increased after the knockout of *FAT1* in the cell lines. Lin et al. found the frequency of *FAT1* mutation rate was high in cases with lymph node metastasis than those without metastasis by analyzing clinical data of 96 patients with HNSCC (21).

The abnormal activation of the Wnt/β-catenin signaling pathway is well established to be a promoter of tumorigenesis and cancer cell proliferation in many types of cancer. The activation of this pathway happens in three steps. Signal transduction at the membrane followed by stabilization of β-catenin in the cytoplasm and activation of Wnt/β-catenin target gene within the nucleus. The downregulation of *FAT1* in HNSCC may be a prominent cause for the dysregulation of the Wnt signaling pathway that leads to aberrant activation of the Wnt/β-catenin signaling pathway, promoting tumor growth. CyclinD1 is the transcriptional target gene in the Wnt/β-catenin signaling pathway, which is involved in the regulation of G1 cell cycle progression and G1/S cell cycle transition(3). *FAT1* inhibits the over-expression of β-catenin promoted cell progression and proliferation, establishing *FAT1*'s role as a tumor suppressor (Fig 2) (2,22).

FAT1 initiates the activation of Hippo kinase cascade via kinase Tao, resulting in phosphorylation of YAP1/TAZ and its degradation by the proteosome. The Hippo/YAP1 pathway is one of the main oncogenic pathways in the majority of cancers, including OSCC.Mutated FAT1 results in unrestrained YAP1 activity that leads to increased cell growth and proliferation in OSCC, which suggests YAP1 is a precision therapeutic option in the treatment of cancers (Fig 2). Adding to the above, YAP1 signaling activates EGFR family members which suggests a link between YAP1 and EGFR Signaling. Further, the YAP1/TAZ/TEAD Transcriptional complex recruits BRD4 and promotes an active chromatin state that controls many oncogenic transcriptional programs in HNSCC (2, 23). Apart from the regulation of EGFR/MAPK by YAP1, *FAT1* mutation also shows its association with increased ERK activity. In addition to the above, a network of other cell surface receptors, such as HER3_Py1289, VEGFR2, PDL1, IGFR signaling mediator IRS 1, and cell-cycle modulator CMYC are associated with FAT1 gene mutation (24). The cytoplasmic domain of FAT1 recruits actin components such as Enabled (Ena)/ vasodilator-stimulated phosphoprotein (VASP) Ena/VASP and Homer1/3 that governs the polymerization of actin complex. Knockdown of *FAT1* decreases the recruitment of endogenous VASP in its leading edge, thus weakening the cytoskeleton controlling cell migration(2).Further, the hypoxic conditions deplete the endogenous *FAT1*, which could also reduce the expression of HIF and its downstream target genes such as CA9, GLUT1, VEGFA, MCT4, HK2, BNIP3, and REDD1(2).

Clinical Significance of _FAT1_ in OSCC

The frequency of *FAT1* gene alteration was found to be 29.8% in HNSCC and more likely to be common in HPV–positive cases when compared to HPV-negative cases. The HNSCC cell lines show a 43% rate of *FAT1* mutation (6). In addition, there is also a significant correlation between *FAT1* mutation and lymph node involvement with disease free survival.Su ll Kim et al. also observed that the five-year overall survival and recurrence-free survival rates were markedly decreased in the *FAT1*-High risk subgroup compared to the *FAT1*-Low risk subgroup (24). Moreover, *FAT1* mutation also stratifies a panel of protein expression in HNSCC cases, which were found to be involved in activating the growth factors and signaling pathways that affect the cancer cell proliferation, metastasis, angiogenesis, and immune-modulation (24). From a clinical perspective, observation of *FAT1* gene mutation in five HNSCC cohorts by Su ll Kim et al. found that *FAT1*-related molecular signature can be considered to be an independent prognostic factor for HNSCC patients. The patients in the *FAT1* low-risk subgroup had a better prognosis than those in the *FAT1* high-risk subgroup, and the prognosis is better observed in HPV negative HNSCC patients than in HPV positive HNSCC patients (24).

The *FAT1* signature and its association to radio sensitivity were also found in HNSCC cell lines. The signature of *FAT1* in HNSCC may help to identify patient's refractory to radiotherapy and to the patients who are in need of intensified or personalized treatment. The patients in the *FAT1*-low risk subgroup shows significant improvement from radiotherapy in comparison to the FAT1-high risk subgroup. The inhibition of YAP1 binding to Scribble is observed in the *FAT1*-high risk subgroup than the *FAT1*-LR subgroup, indicates the higher mutation of *FAT1* relates to higher resistance to radiotherapy (2, 24). Studies on *FAT1*'s significance and its relation in cancer with immune infiltration, as well as its influence on the tumor microenvironment are limited. Significant infiltration of activated dendritic cells is observed in cases with *FAT1* mutation. Genomic and immunologic studies showed patients with *FAT1* mutation have high tumor burden, raised infiltration of

immune cells, and, on the other side, decreased infiltration of immune–suppressive cells and interferons. *FAT1* mutation also elevates growth factors and pro-inflammatory cytokines such as TGFB1, IL-6, and FGF2 (24).

2. CONCLUSION

FAT1 can act as either an oncogene or a tumor suppressor, depending on the type of cancer. The dual function of this gene gains attention in research. For instance, in head and neck squamous cell carcinoma (HNSCC), *FAT1* is frequently mutated and acts as a tumor suppressor. The function of FAT1 further needs to be explored; however, literature studies have shown its role in tumorigenesis and metastasis. The down regulation of *FAT1* has a direct influence on the clinical outcome of the patients with OSCC. With these insights, *FAT1* can be considered as an essential biomarker to be used as a diagnostic and therapeutic biomarker in the treatment of OSCC.

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