Review

Fascin in Gynecological Cancers: An Update of the Literature

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Simple Summary: Fascin, an actin-binding protein, is upregulated in different types of human cancers. It is reportedly responsible for increasing the invasive and metastatic ability of cancer cells by reducing cell–cell adhesions. This review provides a brief overview of fascin and its interactions with other genes and oncoviruses to induce the onset and progression of cancer.

Abstract: Fascin is an actin-binding protein that is encoded by the FSCN1 gene (located on chromosome 7). It triggers membrane projections and stimulates cell motility in cancer cells. Fascin overexpression has been described in different types of human cancers in which its expression correlated with tumor growth, migration, invasion, and metastasis. Moreover, overexpression of fascin was found in oncovirus-infected cells, such as human papillomaviruses (HPVs) and Epstein-Barr virus (EBV), disrupting the cell–cell adhesion and enhancing cancer progression. Based on these findings, several studies reported fascin as a potential biomarker and a therapeutic target in various cancers. This review provides a brief overview of the FSCN1 role in various cancers with emphasis on gynecological malignancies. We also discuss fascin interactions with other genes and oncoviruses through which it might induce cancer development and progression.

Keywords: fascin; gynecological cancer; ovarian cancer; cervical cancer; biomarker

1. Introduction

Fascin, also known as fascin-1 (FSCN1) or actin-bundling protein-1, is a globular filamentous actin-binding protein belonging to the actin cytoskeletal protein family [1]. Molecular cloning techniques showed fascin to be highly conserved during the course of evolution. Furthermore, fascin is homologous to several species, including the Drosophila singed gene [2], Xenopus [3], and mouse [4]. FSCN1 plays a crucial role in the assembly and maintenance of various cellular structures, including filopodia, stress fibers, lamellipodia, invadopodia, dendrites, and spiky protrusions underlying the plasma membrane [5–8]. In addition to its role in maintaining actin structure, FSCN1 regulates several cellular physiological processes, including cell-to-cell interactions, cell-to-matrix adhesion, cell motility, cell migration and invasion as well as focal adhesion dynamics, histone methylation, and gene transcription [9–13].

There are three isoforms of FSCN (FSCN1, FSCN2, and FSCN3) present in humans as well as other vertebrates. Of the three isoforms, FSCN1 is expressed during development in the mesenchymal and nervous tissues and is the most extensively studied form of fascin [14]. On the other hand, FSCN2 is expressed in hair and retinal cells [15,16], while FSCN3 is present in the testis and developing spermatozoa [17]. Both FSCN-2 and -3 are homologous to FSCN-1 by 56% and 29%, respectively.

While in normal tissues there is low or lack of FSCN1 expression, in transformed epithelial cells and carcinomas, it is highly expressed [18]. In different cancers, including colon, pancreatic, breast, lung, esophagus, stomach, skin, and ovarian cancers, elevated
expression of FSCN1 is associated with increased metastatic potential and poor prognosis, indicating its role as a candidate potential biomarker and therapeutic target [19]. Here we discuss the current knowledge of FSCN1 and its underlying mechanisms in order to elucidate its multiple roles in the onset and progression of gynecological cancer.

2. Structure of Fascin

In humans, the FSCN1 (Gene ID: 6624) encodes a distinct 493 amino acid polypeptide and is located on the short arm of chromosome 7, encompassing ~14 kb of DNA including 5 exons.

X-ray crystal structure and sequence analyses revealed FSCN1 to consist of four tandem β-trefoil domains (residues 8–139, 140–260, 261–381, and 382–493) organized as two twisted lobes (β-trefoil 1 and 2; β-trefoil 3 and 4), each of which includes six 2-stranded β-hairpins [20]. Studies demonstrated that all the four β-trefoil domains of FSCN1 play a role in actin binding; while the actin-binding site (ABS)-1 involves the β-trefoil 1 and 4, ABS-2 includes residues from β-trefoil 1 and 2, and ABS-3 involves β-trefoil 3 [21]. Microtubules interact with FSCN1 directly via β-trefoil 2, plausibly inhibiting ABS-1 [12]. The ABS-1 region is located in the first beta-trefoil domain between amino acids 33–47 and consists of a highly conserved site (Ser39) in the center of ABS-1, which can be phosphorylated by protein kinase C (PKC); studies have indicated Ser39 phosphorylation inhibits FSCN1 activity [22,23]. In addition to Ser39, FSCN1 consists of another phosphorylation site, Ser274; mutation of Ser274 to alanine is also involved in inhibiting fascin-bundling activity; however, Ser274 does not lie in the region of ABS1-3 [21,24,25]. On the other hand, ABS-2 consists of two lysine residues (K247/K250) located at the lysine-rich loop at the β-trefoil domain 2 of FSCN1 (between amino acids 241–250) [26]; monoubiquitylation of FSCN1 at K247/K250 stimulates bundle assembly [27]. The postulated location for the other ABS is between amino acids 277–493 [10].

3. Functions of Fascin

Physiologically, FSCN1 is expressed at comparatively low levels in normal cells as compared to malignant cells. Therefore, the distinct roles of FSCN1 in both cell types are important to review.

3.1. Function of Fascin in Normal Cells

As mentioned in the section above, FSCN1 is an actin-bundling protein and crosslinks actin filaments via the three binding sites [5,7,21]. FSCN1 plays a role in the formation and stabilization of several cellular protrusions (microspikes, lamellipodia, and filopodia) [5,7,21] which are essential for cell-to-cell adhesion, cellular interaction, motility, and migration [9–11]. Additionally, FSCN1 also regulates focal adhesion dynamics in multiple types of cells and is partially dependent on the canonical actin-bundling function of FSCN1 [6,12]. Moreover, during normal development, FSCN1 controls cellular processes including cell migration, neurite cone extension, and dendrite formation [19,28,29]. During dendritic cell maturation, FSCN1 is highly expressed; FSCN1-dendritic cells aid in effective interaction and present antigens to T cells, thus playing a vital role in adaptive and innate immunity [30].

On the other hand, FSCN1 binds to microtubule cytoskeleton and regulates focal adhesion dynamics and cell migration [12]. Interruption in FSCN1 and microtubule interaction leads to stability of cell adhesion and reduces cell migration [12]. During cell migration and invasion, FSCN1 interacts with nesprin-2, a nuclear envelope protein to promote nuclear deformation and mobility [31]. Nevertheless, the phosphorylated form of FSCN1 is present in the nucleus and controls histone methylation and gene transcription by interaction with H3K4me3, the H3K4 methyltransferase core subunit RbBP5 form [13]. Nonetheless, FSCN1 regulates extracellular vesicle release [32].

FSCN1 is expressed during mouse embryonic development; however, its expression patterns are widely conserved in human tissues [14,28]. In Drosophila oogenesis, FSCN1
also plays an important role in delamination during border cell migration by modifying the localization of E-cadherin in the border cells [33]. During embryogenesis, as compared to adults, \textit{FSCN1} is significantly expressed during development. In adults, \textit{FSCN1} is absent or at low levels in normal epithelial cells, and its expression is limited to the neuronal, endothelial, mesenchymal, dendritic, and immune cells [18]. During embryogenesis, \textit{FSCN1} is largely expressed in the nervous systems (neuroblasts, melanoblasts, mesenchymal tissue, microcapillary endothelial cells, and antigen-presenting dendritic cells) [18,34,35].

3.2. Function of Fascin in Cancer Cells

When epithelial cells undergo the transformation, \textit{FSCN1} expression levels are highly elevated [36]. \textit{FSCN1} overexpression is documented in the majority of cancers, including ovarian [37], breast [38], colon [39], pancreatic [40,41], glioma [42], melanoma [43], leukemia [44], lymphoma [45], and esophageal squamous cell carcinoma [46]; however, the underlying molecular mechanisms of \textit{FSCN1} activation during the onset and progression of cancer are still understated. Although mutations or amplification of \textit{FSCN1} gene are not common, hypomethylation of \textit{FSCN1} promoter has been found in normal epithelium and cancer cells alike [46], indicating the lack of epigenetic aberration of \textit{FSCN1} in cancer.

The role of \textit{FSCN1} in cancer was first described in breast cancer by Grothey et al. [47], where the authors showed that overexpression of \textit{FSCN1} induced aggressive phenotype. Several additional investigations also reported the role of \textit{FSCN1} in other types of cancer and its association with an aggressive phenotype, poor prognosis, and short survival [19,36,48,49]. An earlier study found significant overexpression of \textit{FSCN1} in human epithelial tumors (lung, cervical, ovarian, esophageal, pancreatic, gastric, hepatocellular, colorectal, breast, nasopharyngeal, and laryngeal carcinomas) in comparison with their corresponding normal tissues, leading to the conclusion that overexpression of \textit{FSCN1} correlates with tumor occurrence and progression [50]. In this regard, it was found that \textit{FSCN1} can promote cancer progression through both canonical and non-canonical pathways by triggering cancer proliferation, migration, invasion, and metastasis [19,36].

There are several functions by which \textit{FSCN1} promotes cancer progression via inducing cancer cell growth, proliferation, migration, invasion, and metastasis [19,36]. In vitro findings reported contrasting roles of \textit{FSCN1} in cell growth and proliferation. While upregulated expression of \textit{FSCN1} was found to be correlated with enhanced cell proliferation in different cancer cell lines [51–53], few studies reported no significant cell proliferation in \textit{FSCN1}-transduced cancer cells [54,55]. While one study in the aggressive breast cancer cell line, MDA-MB-231, reported stimulated \textit{FSCN1} expression to provoke cell proliferation [51], other investigations by Al-Alwan et al. [56] and Heinz et al. [57] did not report a significant effect of transduced \textit{FSCN1} expression on MDA-MB-231 cell proliferation. Similarly, in the non-small lung cancer cell line, A549, it was reported that enhanced \textit{FSCN1} has a light impact on cell proliferation [58]; however, another study using A549 cells reported that \textit{FSCN1} could enhance cell proliferation via the YAP/TEAD signaling pathway [52]. Moreover, knockdown of \textit{FSCN1} leads to the inhibition of the A549 cell growth and proliferation via the MAPK signaling pathway [59].

On the other hand, one of the principal functions of \textit{FSCN1} contributions to cancer progression is the actin-bundling function [6]. Alterations in the dynamics of microtubules, including their expression and stability, have been shown to lead to cancer invasion and metastasis [57,60]. \textit{FSCN1} also facilitates mechano-transduction by interaction with the LINC complex, which is responsible for cell invasion and migration [31,61,62]. The other function includes the role of \textit{FSCN1} within the nucleus to control nucleolar size and morphology [63], in addition to nuclear actin [64,65], chromatin regulation, and assembly [13]. Thus, deregulation in these functions contributes to cancer development and progression [65–67]. Additionally, \textit{FSCN1} also regulates oxidative phosphorylation of the mitochondria and metabolic stress resistance, thus inducing cancer metastasis [54].

Moreover, in vitro data also demonstrated the role of \textit{FSCN1} in inducing cancer cell migration by promoting filopodia formation and epithelial-mesenchymal transition
(EMT) [68] in various cancer cells, including ovarian [37], oral [53], hypopharyngeal [69], osteosarcoma [70], and pancreatic cancer cells [41]. FSCN1 induces filopodia and invadopodia stability and formation [7]. In addition, it enhances the expression of matrix metalloproteinases (MMPs) [41,69], thus promoting cancer cell motility and invasion. On the other hand, in vivo studies using different models also reported FSCN1-induced migration and invasion. In mouse and zebrafish models, FSCN1 expression was found to induce colon tumor invasion [71,72]. Similarly, breast cancer in vivo models reported elevated FSCN1 expression to induce cancer cell metastasis to the lung [40]. In nude mice models, overexpression of FSCN1 was linked with metastasis in pancreatic [73], renal [74], and colorectal carcinomas [75]. Additionally, in severe combined immunodeficiency (SCID) mice, enhanced FSCN1 expression provoked lung metastasis in osteosarcoma cells [70]. Furthermore, previous studies reported that FSCN1 could promote cancer progression by inducing chemoresistance in cancer cells as well as controlling metabolism and contributing to a de-differentiated and more stem-like state [76].

### 3.3. Mechanisms of Fascin Deregulation

Numerous transcriptional factors (TFs) interact and bind to the FSCN1 promoter regions, thus regulating FSCN1 expression. It was reported that FSCN1 transcriptional activity is controlled by the promoter region (−219/+114); in breast and colon cancer, CREB and aryl hydrocarbon receptors (AhRs) bind with the −219/+114 promoter region [77]. On the other hand, in human oral cancer, Lee et al. [78] reported that interleukin (IL)-1β triggered phosphorylation of several key players, including CREB, ERK1/2, JNK, and NF-κB, thereby inducing FSCN1 expression and promoting invasion (Figure 1). Furthermore, cytokines (IL-6 or tumor necrosis factor-alpha (TNF-α) trigger the NF-κB and STAT3 pathways, which are essential for enhancing FSCN1 expression in cancer [79–81] (Figure 1). In gastric cancer, one study reported that Fas signaling induces FSCN1 expression via the STAT3 pathway [82]; another study demonstrated that galectin-3 regulates the GSK-3β/β-catenin/TCF-4 signaling pathway, thus triggering FSCN1 expression [83] (Figure 1). In colorectal cancer, the β-catenin-TCF signaling pathway was reported to regulate FSCN1 transcription [84]; however, the studies in breast and colon cancer failed to report the regulation of FSCN1 expression via β-catenin-TCF signaling [77,85]. Another study in colorectal cancer demonstrated loss of p53 to induce FSCN1 expression via the NF-κB pathway [86] (Figure 1). Moreover, in esophageal squamous cell carcinoma, overexpression of the epidermal growth factor (EGF) increased specificity of protein 1 (Sp1) phosphorylation and activated the ERK1/2 pathway, thus enhancing FSCN1 expression [87] (Figure 1). Furthermore, the snail family of transcription factors was reported to be involved in FSCN1 transcription; SNAIL2 expression induced FSCN1 expression in human colon and pancreatic cells [40]. In head and neck cancer cells, SNAIL2 was found to directly bind to the FSCN1 promoter, inducing FSCN1 expression (Figure 1) [88]. On the other hand, in hypopharyngeal and pancreatic cancers, HIF-1α was reported to induce the overexpression of FSCN1 [41,69] (Figure 1). Nevertheless, a study by Megrioni and colleagues [89] demonstrated the overexpression of FSCN1 in NT2 cells, known to be deficient of the CREB-binding protein during neurogenesis, indicating a viral role of FSCN1 in the formation of mature neurons (Figure 1).

Similar to transcription factors regulating FSCN1 expression, microRNAs (miRNAs) are known to bind to the 3′ untranslated region (UTR) of FSCN1 and regulate its expression in several human cancer tissues and cell lines, including breast, lung, liver, colon, cervix, prostate, pancreatic, hepatocellular, esophageal, and nasopharyngeal [90–101]. On the other hand, loss of miRNAs -133a and -145 was found to enhance FSCN1 expression, thus stimulating cancer cell growth, proliferation, migration, and invasion along with the inhibition of apoptosis [90–94,96–101]. In addition, FSCN1 is directly targeted by several miRNAs in different cancers. Thus, miRNA-24 targets FSCN1 in nasopharyngeal and prostate cancer [95,102], FSCN1 is targeted by miRNA-143 in esophageal [103] and miRNA-326 in lung and gastric cancers [104,105], respectively. Yu et al. demonstrated that the
loss of miRNA-663 in colorectal cancer cells induced FSCN1 expression [106]. Chen et al. reported overexpression of miRNA-451 to enhance FSCN1 expression via the inhibition of AMPK and activation of mTOR signaling [107].

Figure 1. Mechanisms of FSCN1 deregulation. Several factors, including EGFR, TGF-β, and interleukins, in addition to oncoviruses, trigger key pathways including CREB, ERK1/2, JNK, STAT3, PI3K, MAPK, and NF-κB to deregulate FSCN1 expression and stimulate underlying mechanisms for cancer progression.

3.4. Role of Oncoviruses in Fascin Deregulation

Previous studies have shown potential deregulation of FSCN1 via viral oncogenesis (Figure 1). In this regard, overexpression of FSCN1 was reported in Epstein-Barr virus (EBV)-induced lymphoblastoid cell lines [108]. More specifically, LMP1, one of the oncoproteins of the EBV, was found to stimulate FSCN1 in lymphocytes via NF-κB signaling, contributing to lymphocyte migration and invasion [44]. While FSCN1-negative Hodgkin's lymphoma-derived cell lines also show upregulated FSCN1 levels [44], LMP1-negative Burkitt lymphoma-derived cell lines are negative for FSCN1 expression [109]. Moreover, a study by Liu et al. in EBV-positive nasopharyngeal carcinoma reported that enhanced LMP1 levels and phosphorylated STAT3 elevated FSCN1 expression and was associated with lymph node metastasis and higher proliferation index of the cancer cells [110]. Since LMP1 is present in epithelial cells and is known to have a potential role in EBV production [111], continuous expression of FSCN1 can help in EBV release. Moreover, the transmission of EBV to epithelial cells is dependent on NF-κB signaling [112], which is one of the major factors for effective FSCN1 induction. LMP1 of EBV can induce expression of FSCN1 at both mRNA and protein levels in lymphocytes [113]. Studies by Mohr et al. [44,113] demonstrated that the inhibition of NF-κB signaling using a chemical inhibitor of IκB kinase β (IKKβ) or cotransfection of a dominant-negative inhibitor of IκBα (NFKBIA) decreased both FSCN1 levels and the invasive ability of EBV-transformed lymphoblastoid cells. Moreover, the study showed that the knockdown of FSCN1 by two different small hairpin RNAs reduced invasion of lymphocytes [113]. Similarly, in LMP1-positive Jurkat T lymphocytes, FSCN1 is reported to induce cell migration [114]. In colorectal cancer, upregulated FSCN1 expression was reported in LMP1-positive samples and was associated
with moderately to poorly differentiated adenocarcinomas [115]. The study suggested that Wnt/β-catenin signaling regulates epithelial-mesenchymal transition (EMT) induced by FSCN1 in LMP1-positive cancers to provoke cancer progression (Figure 1) [115]. Likewise, in EBV-associated gastric cancer, upregulated Smad4/FSCN1 expression significantly correlated with larger tumor size, higher histological grade, lymph node involvement, vascular invasion, and poor clinical outcome [116].

FSCN1 upregulation was also correlated with other oncoviruses. Kress et al. [117] reported that Tax, the oncoprotein of leukemia-inducing retrovirus HTLV-1, could upregulate FSCN1 expression through the regulation of the NF-κB signaling pathway (Figure 1). A recent study in adult T-cell leukemia/lymphoma (ATLL) with HTLV-1–infected Hodgkin and Reed-Sternberg–like cells found elevated FSCN1 expression [118]. Gross and colleagues [119] further found FSCN1 to play a vital role in the transport of viral proteins to budding sites and promote HTLV-1 transmission.

FSCN1 was also reported to be associated with high-risk HPV to enhance cancer progression. It is well-known that high-risk HPVs are major players in the onset and progression of cervical cancer and correlate with lymph node and vascular invasion and the tumor size [120,121]. More specifically, Yasmeen et al. [122] investigated the expression of oncogenes, including FSCN1, in cervical cancer. In this study, the use of Src/Abl inhibitor in HPV-positive cervical cancer cell lines (SiHa and HeLa) was found to restore β-catenin accompanied by the downregulation of FSCN1 expression pattern, thus inhibiting cell invasion ability of these cancer cell lines [122]. In addition, a study in Iran was carried out to investigate the prevalence of HPV and FSCN1 in cervical squamous cell carcinoma and found an association between FSCN1 overexpression and HPV positivity [123]. The association of HPV with FSCN1 was also reported by our group [124], where we demonstrated that E6/E7 oncoproteins of HPV is associated with FSCN1 overexpression in human colorectal cancer. These studies clearly show that human oncoviruses can deregulate the expression patterns of FSCN1, thereby promoting cancer progression (Figure 1).

4. Fascin in Gynecological Cancers

Numerous studies have reported overexpression of FSCN1 in various gynecological cancers [123,125–147] as indicated in Table 1.

| Type of Cancer | Detection Method (Assay) | Clinicopathological Features | References |
|---------------|--------------------------|-------------------------------|------------|
| Ovarian Cancer | IHC                      | Poor overall survival and prognosis | [127]     |
|               | IHC                      | Serous subtype, micropapillary pattern, FIGO stage, and risk of recurrence | [128]     |
|               | IHC                      | Serous subtype and residual postoperative tumor | [130]     |
|               | ICC and IHC              | Involved with intraperitoneal invasion | [131]     |
|               | IHC                      | Presence of vascular invasion, psammomatous calcifications, and lymphocytic infiltration | [132]     |
|               | IHC                      | -                             | [134]     |
|               | IHC and WB               | Tumor aggressiveness          | [137]     |
|               | IHC                      | -                             | [125]     |
|               | IHC                      | -                             | [126]     |
|               | IHC                      | T and N-stage, AJCC clinical stage, and poor survival rate | [138]     |
|               | IHC                      | Advanced TNM stage, poor histological differentiation, and poor survival rate | [139]     |
|               | IHC and IF               | Invasion and migration, metastasis, colonization, and poor prognosis | [140]     |
|               | IHC                      | Tumor grade and tumor aggressiveness | [147]     |
Table 1. Cont.

| Type of Cancer | Detection Method (Assay) | Clinicopathological Features | References |
|----------------|--------------------------|-----------------------------|------------|
| Endometrial Cancer | IHC                      | Tumor grade and neural invasion | [129]       |
|                 | IHC                      | High tumor grade            | [133]       |
|                 | IHC                      | Tumor aggressiveness, distant metastasis, and local recurrence | [141]       |
|                 | IHC                      | Lymphovascular space invasion and epithelial-mesenchymal transition | [143]       |
|                 | IHC                      | Higher expression in leiomyosarcoma | [135]       |
|                 | IHC                      | Extrapelvic disease, higher stage, larger tumor size, shorter progression-free interval, and reduced ER-α expression | [142]       |
| Vulvar Cancer   | IHC                      | -                           | [145]       |
| Cervical Cancer | IHC                      | Increased invasivion         | [136]       |
|                 | IHC                      | Tumor invasion               | [144]       |
|                 | NM-PCR and IHC           | HPV overexpression           | [123]       |

ICC: immunocytochemistry; IF: immunofluorescence; IHC: immunohistochemistry; NM-PCR: nested multiplex polymerase chain reaction; WB: Western blot.

4.1. Fascin in Ovarian Cancer: A Candidate Biomarker and Potential Therapeutic Target

A previous report revealed higher FSCN1 expression in borderline and malignant ovarian tumors as compared to benign cases; however, no significant difference was reported between FSCN1 staining in borderline and malignant cases [147]. In contrast, another investigation reported enhanced expression of FSCN1 in primary, borderline, and metastatic ovarian cancers compared with the normal ovarian tissues where no FSCN1 expression was observed. The authors found that FSCN1 expression was associated with the increased risk of intraperitoneal tumor growth and spread [131]. In addition, the authors detected elevated FSCN1 expression in cell cultures derived from patients with stage IV ovarian cancer compared with cell cultures derived from stage II-III ovarian cancer patients [131]. In another study, Daponte et al. [127] showed FSCN1 expression in advanced poorly differentiated serous ovarian cancer that was associated with poor prognosis, suggesting FSCN1 as an independent prognostic biomarker. More interestingly, an IHC analysis using TMAs to analyze the expression of six EMT biomarkers (FSCN1, cortactin, survivin, EGFR, MMP-2, and MMP-9) in serous carcinomas, mucinous carcinomas, endometrioid adenocarcinomas, and clear cell carcinomas found significant expression of only FSCN1, cortactin, survivin, and EGFR [138]. The study also reported higher scoring for FSCN1 in mucinous carcinomas, which was associated with TNM stage and poorer survival rate [138]. Another study also reported upregulated expression of FSCN1, cortactin, and EGFR in TMAs of four ovarian carcinomas (serous carcinoma, mucinous carcinoma, endometrioid adenocarcinoma, and clear cell carcinoma) [139]. Moreover, FSCN1 overexpression was associated with advanced cancer stage, poorer histological differentiation, and survival rate of mucinous carcinoma, suggesting a potential role of FSCN1 as a candidate biomarker for aggressive serous and mucinous carcinomas [139]. On the other hand, previous studies also reported overexpression of FSCN1 in epithelial ovarian cancer and indicated the interaction between cell and matrix as a vital step in the progression of malignant epithelial ovarian neoplasms [130,134]. Moreover, high FSCN1 scoring was associated with poorer tumor differentiation in serous, mucinous, and endometrioid adenocarcinoma, indicating a role of FSCN1 in analyzing tumor aggressiveness, and was suggested as an independent prognostic risk factor in mucinous carcinoma [138]. Similarly, Coa et al. [126] revealed enhanced expression of FSCN1 in primary mucinous carcinomas in comparison with borderline mucinous tumors with a significant expression in metastatic tumors as compared with primary tumors. Furthermore, while FSCN1 expression was significantly upregulated in
borderline and malignant ovarian tumors, there was no expression of FSCN1 in benign ovarian tumors [125]. Another immunohistochemical study revealed that a strong FSCN1 positivity was associated with serous subtype and micropapillary growth pattern [128]. Another investigation by Kostopoulou et al. [137] analyzed the expression of FSCN1 in ovarian cancer using IHC and Western blotting and reported an upregulation of FSCN1 expression in invasive ovarian carcinomas as compared with borderline tumors and cystadenomas. In addition, the study pointed out an association between FSCN1 overexpression and advanced stage and aggressive phenotype [137]. Thus, evaluating FSCN1 expression as a biomarker depicting the progression and outcomes of several types of gynecological cancers has been the center of renewed interest. Another investigation found significantly higher stromal FSCN1 expression in borderline and malignant epithelial ovarian tumors in comparison to normal ovaries and benign epithelial ovarian tumors [132].

McGuire and colleagues showed that the silencing of FSCN1 in ovarian cell lines (HeyA8, Ovcar5, and Tyk-nu), primary human cancer-associated fibroblasts and primary human omental mesothelial cells reduced metastasis [140]. TMA analysis showed higher FSCN1 expression in the tumor stroma than in cancer compartments, and this was associated with the advanced tumor stage [140]. In vitro and in vivo data showed that the loss of FSCN1 significantly inhibited trans-mesothelial migration of the ovarian cancer cell line ES-2 and reduced the interaction between ovarian cancer cells and mesothelial cells in the mouse peritoneal cavity [148]. Moreover, overexpression of FSCN1 in SKOV3 (ovarian cancer cell line) triggered trans-mesothelial migration [148]. On the other hand, in mature and immature neural components, the expression of FSCN1 was detected regardless of rosette formation in immature teratomas derived from both human ovary stem cells, indicating FSCN1 immunostaining as a potential biomarker in diagnosing and grading human immature teratomas [146].

A recent study examined the effect of curcumin against FSCN1 in the ovarian cancer cell line SKOV3 and found curcumin to inhibit STAT3 via the JAK/STAT3 signaling pathway. Notably, the inhibition of STAT3 also led to FSCN1 activity inhibition [149]. In addition to blocking FSCN1, in curcumin-exposed ovarian cancer cells, the formation of filopodia was disrupted, and cell migration was reduced [149]. Recently, Yoshihara et al. [148] documented the importance of filopodia in the trans-mesothelial migration of ovarian cancer cells. Additionally, in athymic nude mice, FSCN1 activity was inhibited therapeutically with the compound G2 [140]. The treatment inhibited the actin-bundling into stress fibers as well as ovarian cancer cell migration by reducing GTP-bound Cdc42 and Rac1, further indicating a therapeutic role of G2 in ovarian cancer [140,150].

4.2. Fascin in Endometrial Cancer: A Potential Biomarker and Therapeutic Target

Similar to ovarian cancer, studies were performed to detect FSCN1 expression in uterine cancer. Uterine carcinosarcoma cases were assessed for FSCN1 expression using IHC; while FSCN1 was absent in benign cases, it was present in both malignant epithelial and mesenchymal elements of uterine carcinosarcomas. This finding was associated with a more aggressive phenotype (advanced stage and large tumor size) and a poor outcome [142]. Additionally, FSCN1 was found to be a potential IHC biomarker in differentiating uterine leiomyosarcoma from leiomyoma [135]. In undifferentiated endometrial carcinomas, the studies reported a loss of E-cadherin and β-catenin and overexpression of FSCN1, galactin-3, cyclin D1, and p16, which is involved in EMT and invasion, thus contributing to aggressive behavior and poor prognosis [141,143,151]. Another investigation revealed significant overexpression of FSCN1 in proliferative endometrial carcinoma samples as compared with the control samples with a significant association with tumor grade and neural invasion [129]. In another report, Kabukcuoglu et al. [133] showed that during endometrial neoplasia development, there was a loss of stromal FSCN1 expression and its increase in the epithelial compartment; this finding was associated with tumor grade and overall survival. The overexpression of FSCN1 protein was also reported in
vulvar cancer; however, immunostaining failed to distinguish in situ from invasive lesions as well as putative HPV-associated and HPV-independent squamous cell carcinomas [145].

4.3. Fascin in Cervical Cancer: A Potential Biomarker and Therapeutic Target

In spite of the confirmed role of FSCN1 in several human carcinomas, there has been a limited number of investigations pertaining to the presence and role of FSCN1 in cervical cancers. In this context, Stewart et al. analyzed FSCN1 expression by IHC in in situ and invasive adenocarcinoma of the endocervix and found FSCN1 overexpression to occur during the development and progression of some endocervical neoplasms, indicating the role of FSCN1 in tumor invasion [144]. Koay et al. [136] reported the expression pattern of FSCN1 in cervical carcinoma by IHC; the normal endocervical epithelium was negative for FSCN1, while the normal squamous epithelial stained positive for FSCN1 in basal and parabasal cells [136]. Furthermore, cervical endothelial cells had constant FSCN1 staining, whereas, in CIN lesions and invasive squamous cell carcinomas, there was high FSCN1 expression [136]. Both studies indicate FSCN1-induced invasion in cancer cells due to loss of cell-to-matrix adhesion [132,136]. In addition, in our laboratory, we found FSCN1 to be overexpressed in cervical cancer tissue (Figure 2).

![Figure 2. Fascin expression in cervical cancer (A,B). A case of invasive squamous cell carcinoma of the uterine cervix: (A) hematoxylin and eosin slide (20 ×) with diffused and strong immunohistochemical expression of the fascin protein in cancer cells (B, 20 ×).](image)

5. Fascin in Other Cancers

Several previous studies analyzed FSCN1 expression using PCR and immunohistochemistry (IHC), revealing its increased expression compared to normal tissues. A systematic review and meta-analysis of studies analyzing the relevance of FSCN1 in five different carcinomas (breast, colorectal, esophageal, gastric, and lung) by IHC reported that FSCN1 correlates with a high risk of disease progression in breast and colorectal cancers [48]. They also noted that FSCN1 expression is associated with a high risk of mortality in breast, colorectal, and esophageal cancers. Moreover, FSCN1 expression is linked with a high risk of distant and lymph node metastasis in colorectal and gastric carcinomas [48].

Of the gastrointestinal cancers, esophageal cancers has the worst prognosis. FSCN1 is involved in the pathogenesis and metastasis of esophageal carcinoma; high FSCN1 expression increases gradually from the normal to the invasive form and correlates with cell proliferation, lymph node invasion, metastasis, and high tumor stage [152–156]. Moreover, overexpression of FSCN1 is associated with poor overall and disease-free survival [155]. On the other hand, gastric carcinoma studies using TMA and IHC reported FSCN1 overexpression at both mRNA and protein levels [157,158]; high FSCN1 expression is associated with tumor size, poorly differentiated tumors, invasion, metastasis, TNM stage, and poor...
survival [157,159–163]. In the colon as well, FSCN1 expression is higher in sporadic and familial colorectal adenomas and adenocarcinomas as compared to the healthy colon [164]. FSCN1 expression was reported to progress from focal during the early stages to diffused in the advanced stages [165]. Increased FSCN1 expression is associated with poor clinicopathological outcomes including advanced tumor stage, grade, and lymph node invasion with poor overall survival and disease-free survival rates [48,166,167]. Therefore, FSCN1 is suggested as a poor prognostic marker for regional and distant metastasis [167,168]. Moreover, FSCN1 expression is also reported in K-ras mutant tumors [169]. FSCN1 expression is also higher in hepatocellular carcinoma tissues compared with normal liver tissues which significantly correlates with the tumor grade, lymph node invasion, and distant metastasis in addition to poor prognosis [170–172]. However, a study by Lin et al. showed no correlation between FSCN1 overexpression and clinicopathological features [171]. Similar to all gastrointestinal cancers, in pancreatic cancer, there is an increase in FSCN1 expression during carcinogenesis progression (from pancreatic intraepithelial neoplasia to pancreatic adenocarcinoma); high FSCN1 expression correlates with higher histological grades, and poor overall survival [40,41,173].

While lymphocytes, myeloid, and plasma cells stain negative for FSCN1, in human hematologic malignancies including HIV-related lymphoid hyperplasia, Reed-Sternberg cells, Hodgkin’s lymphoma, Castleman’s disease, and other lymphoid hyperplasia, FSCN1 is overexpressed [174,175]. A study by El Kramani et al. [176] determined FSCN1 levels in with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) cases in comparison to controls using enzyme-linked immunosorbent assay in the plasma and leukocytes and found FSCN1 expression significantly elevated in AML but not in ALL cases, suggesting FSCN1 as a potential biomarker for AML. Another study analyzed differential expression of FSCN1 in classic Hodgkin lymphoma (CHL), anaplastic large cell lymphoma (ALCL), and diffused large B-cell lymphoma (DLBCL); the study showed that FSCN1 is significantly upregulated in CHL as compared to DLBCL and ALCL, indicating a role of FSCN1 in the differential diagnosis of CHL against ALCL and DLBCL [177].

6. Therapeutic Potential of Fascin

Due to the ability of FSCN1 to induce cell migration, invasion, and metastasis, FSCN1 is a potential candidate molecule for anti-cancer or anti-metastatic therapy in human cancers [19,36,48,50,73,115,178]. Several targets for FSCN1 are being developed and include miRNA, siRNA, shRNA, small molecule inhibitors, and nanobodies [73,91–97,99,140,150,179–189].

In multiple types of cancers, in vitro studies demonstrated that overexpression of miRNAs targeting FSCN1 in cancer cell lines reduce cell growth, proliferation, migration, and invasion [91–95,97,99], thus indicating miRNAs or miRNA-based reagents as potential therapeutic options. On the other hand, siRNAs specifically degrade targeted mRNA; in vitro and in vivo studies reported FSCN1 knockdown by siRNA leading to decreased cell migration and metastasis, respectively [54,73,140,150,182,183]. Over the last 10 years, more than 50 therapeutic RNAi-based drugs entered phase-I, II, and III trials, of which 15 phase-I, II, and III programs are dedicated to cancer treatment [190]. While miRNAs and siRNAs can be developed as therapeutics for metastatic cancers, there are several limitations in their role in clinical settings. Overcoming the key challenges, including adverse side-effects, delivery systems and administration paths, dosage concerns, and off-target effects, is necessary to develop RNAi-based therapies for cancer and other diseases [191]. Multiple immune-related side-effects and severe hyperbilirubinemia were some of the adverse events that developed during clinical trials of miRNA-based therapies [192–194]. Even though several preclinical studies use mouse models of cancer, only few miRNA candidates have reached clinical phases. Further investigations, including pharmokinetic studies in animal models, are essential to understand the role of RNAi-based therapies in humans [191]. On the other hand, nanotechnology aims to provide multipurpose platforms to allow safe biomolecule delivery, enhance therapeutic efficacy, reduce drug dosage, and minimize adverse events [195]. However, these systems are yet to reach human trial
phase as nanocarrier application is dependent on various parameters (average diameter, charge, shape, surface chemistry, and polydispersity index) [195]. In solid tumors, although nanoparticles are stabilized, their mechanistic entry is more complex plausibly due to the involvement of trans-endothelial pathways [196,197]. Moreover, establishing the optimal dose in RNAi-based therapy is complex as treating patients with either a non-active or potential toxic dose is unethical [191]. Since initial doses for phase I/II trials are derived from in vitro and in vivo data (preclinical), various variables including size, volume, immune response, administration routes, and toxicity are major areas of concern [191,198]. It is worth noting that, while RNAi-based therapy is frequently administered intravenously or subcutaneously, development of oral therapy is essential for clinical trials [199]. Finally, RNAi-based therapeutics come with a high cost to cover both RNAi-based products and emerging nanocarriers as compared to prevailing anti-cancer therapeutics; therefore, the cost–benefit ratio is another challenge involved in this kind of therapy [200].

Experiments using inhibitory nanobodies against FSCN1 protein showed disruption of the FSCN1/actin-bundling [187]. Although in vitro studies using FSCN1-specific nanobodies in breast (MDA-MB-231) and prostate (PC3) cancer cells inhibited the formation of invadopodium and cell invasion [187], the use of FSCN1-specific antibodies in clinical settings needs to be established. Moreover, series of thiazole derivatives, isoquinolone, and pyrazolo[4,3-c] pyridine were also reported to be potential inhibitors of metastasis by targeting FSCN1 [181,189].

Likewise, small molecule inhibitors can reduce tumor cell migration and invasion and help pave the way against FSCN1-induced tumors [75,179,184–186]. In ovarian cancer, Wang et al. treated the ovarian cancer cell line (ES-2) with a Leucine aminopeptidase 3 (LAP3) inhibitor, bestatin [188]. Bestatin was found to significantly inhibit tumor cell migration and invasion by blocking FSCN1 promoter and reducing its expression, thus acting as a plausible anti-metastatic therapeutic agent [188]. Other studies have shown that migrastatin and its analogues target FSCN1 and block its activity, thereby reducing cell migration, invasion, and tumor metastasis [179,185]. In addition to migrastatin, another investigation in colorectal cancer cells showed an antimigratory and anti-invasive effect of imipramine (anti-depressant) by inhibiting FSCN1 activity [75], thus introducing a novel molecular targeted treatment in FSCN1-induced tumors. A novel small molecule compound G2 and its derived analogs (NP-G2-011, NP-G2-036, NP-G2-044, and NP-G2-050) were tested and displayed anti-metastatic properties along with enhanced response and survival in in vivo models by blocking FSCN1 activity [184,186]. Recently, the phase 1A clinical trial in ovarian cancer patients was carried out to evaluate the dosage and safety of NP-G2-044; the drug was administered daily as a single oral dose (200–2100 mg) for 6 weeks, including four weeks of daily dosing and two weeks rest period [180]. While no dose-limiting toxicity and fatality were reported, the trial demonstrated the inhibitor (NP-G2-044) as a safe single-drug, with a daily dose of 1600 mg as the provisional recommended phase 2 dose [180]. Prior to treatment with the drug (NP-G2-044), ovarian cancer patients with metastasis to visceral organs were treated with anti-cancer therapeutic drugs. Treatment with NP-G2-044 showed a comparably better treatment efficacy as compared to treatment with anti-cancer therapeutic modalities [180]. Moreover, the drug displayed anti-tumor and anti-metastatic properties including progression-free-survival and metastasis-free interval, particularly for metastatic ovarian cancer patients [180]. Proposed future studies include a phase 2A clinical trial to assess the efficacy of NP-G2-044 at the identified dose (1600 mg), both in monotherapy as well as in combination with anti-PD-(L)1 immune checkpoint inhibitors [180]. Table 2 summarizes anti-fascin-based therapeutic approaches.

Since FSCN1 can stimulate cancer cell migration and metastasis, there are several limitations in developing therapeutic targets against FSCN1. While FSCN1 is not expressed in adult epithelial tissues, it is normally expressed in other adult non-epithelial tissues [14], raising the concern that FSCN1 inhibitors may have negative side effects. Specifically, the inhibition of FSCN1 may cause neuronal, kidney, endocrine, wound healing, and immune defects.
### Table 2. Anti-fascin-based Therapeutic Approaches.

| Therapeutic Approach                             | Outcome                                                                                   | Reference |
|-------------------------------------------------|-------------------------------------------------------------------------------------------|-----------|
| FASNb5 (Fascin nanobody, Kd~35 nM, 1:1 stoichiometry) | Invadopodium instability                                                                  | [187]    |
| CORNb2 (Cortactin nanobody, Kd~75 nM, 1:1 stoichiometry) | Blocks invadopodium precursor formation and MMP secretion                                  | [187]    |
| Migrastatin and its analogues                   | Inhibits cell migration, invasion, and metastasis                                         | [179,185]|
| Thiazole derivatives                            | Inhibits cell migration and suppresses angiogenesis                                       | [189]    |
| Bestatin (LAP3 inhibitor)                       | Inhibits FSCN1 expression and suppresses tumor cell migration and invasion in a dose-dependent manner | [188]    |
| Isoquinolone and pyrazololo[4,3-c]pyridine inhibitors | Disrupts actin binding                                                                  | [181]    |
| G2 compound                                     | Inhibits actin structures, migration, and invasion of cancer cells                        | [186]    |
| NP-G2-044                                       | Increase in duration of treatment, progression-free-survival, and metastasis-free interval. Displays anti-tumor and anti-metastatic activity | [180,184]|
| NP-G2-044 and PD-L1 inhibitor                   | In progress                                                                               | [180]    |
| Curcumin                                        | Blocks fascin expression through JAK/STAT3 pathway downregulation. Inhibits cell attachment, invasion, and migration | [149]    |

### 7. Conclusions

FSCN1 is regulated by several signaling pathways (AMPK/mTOR, Wnt/β-catenin, and MAPK) and is overexpressed in various human carcinomas including gynecological cancers; however, understanding the exact molecular mechanisms underlying FSCN1 deregulation and interaction with other genes and oncoviruses, especially in gynecological cancers, is still nascent. Although several studies have indicated a potential diagnostic utility of FSCN1, its therapeutic role as an anti-cancer target is still under investigation. We believe that further studies are needed, including the development of conditional transgenic and/or knockout animal models, to determine the role of FSCN1 targeting as a potential therapeutic route for gynecological carcinomas.

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**Abbreviations**

Abl: Tyrosine-protein kinase ABL1; ABS: actin-binding site; AhR: aryl hydrocarbon receptor; ALCL: Anaplastic large cell lymphoma; ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; AMPK: 5′ adenosine monophosphate-activated protein.
kinase; Cdc: Cell division control protein 42 homolog; CHL: Classical Hodgkin lymphoma; CREB: cAMP-response element binding protein; DLBCL: Diffuse large B-cell lymphoma; EBV: Epstein-Barr virus; EGF: Epidermal growth factor; EGFR: Epidermal growth factor receptor; EMT: Epithelial-mesenchymal transition; ERK: Extracellular regulated kinase; FSCN: Fascin; GSK-3β: Glycogen Synthase Kinase-3 Beta; GTP: Guanosine triphosphate; HIF-1α: Hypoxia-inducible factor-1-alpha; HPV: Human papillomavirus; HTLV-1: Human T-lymphotropic virus type-1; IHC: Immunohistochemistry; IL: Interleukin; JNK: c-Jun N-terminal kinase; kDa: Kilo Dalton; LAP3: Leucine aminopeptidase 3; LMP: Latent membrane protein; MAPK: Mitogen-activated protein kinase; miRNA: microRNA; MMP: Matrix metalloproteinase; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor kappa light chain enhancer of activated B cells; NT2: NTERA-2; Rac1: Ras-related C3 botulinum toxin substrate 1; SCID: Severe combined immunodeficiency; Ser: Serine; shRNA: Small hairpin RNA; siRNA: Small interfering RNA; SMAD4: SMAD family member 4; STAT3: Signal transducer and activator of transcription 3; TCF: T-cell factor; TEAD: Transcriptional enhanced associate domain; TFs: Transcription factors; TMA: Tissue microarray; TNF: Tumor necrosis factor; UTR: Untranslated region; Wnt: Wingless; YAP: Yes-associated protein.

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