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NARRATIVE REVIEW

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Role of fibrilins in human cancer: A narrative review

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Abstract

Background: Fibrillin is one of the extracellular matrix glycoproteins and participates in forming microfibrils found in many connective tissues. The microfibrils enable the elasticity and stretching properties of the ligaments and support connective tissues. There are three isoforms of fibrillin molecules identified in mammals: fibrillin 1 (FBN1), fibrillin 2 (FBN2), and fibrillin 3.

Objective: Multiple studies have shown that mutations in these genes or changes in their expression levels can be related to various diseases, including cancers. In this study, we focus on reviewing the role of the fibrillin family in multiple cancers.

Methods and Results: We performed a comprehensive literature review to search PubMed and Google Scholar for studies published so far on fibrillin gene expression and its role in cancers. In this review, we have focused on the expression of *FBN1* and *FBN2* genes in cancers such as the lung, intestine, ovary, pancreatic ductal, esophagus, and thyroid.

Conclusion: Altogether various studies showed higher expression of fibrillins in different tumor tissues correlated with the patient's survival. However, there are controversial findings, as some other cancers showed hypermethylated *FBN* promoters with lower gene expression levels.

KEYWORDS
cancer, ECM, fibrillin 1, fibrillin 2

1 | INTRODUCTION

Identifying novel biomarkers is a foundation for cancer diagnosis and the development of therapeutic strategies.[1–3] Fibrillins (FBNs) are large glycoproteins with supramolecular fibrous structures in the extracellular matrix (ECM).[4–6] Fibrillin proteins with other molecules assemble together to form microfibrils within the ECM.[7–9] In the structure of microfibrils, the fibrillins are connected head-to-tail in parallel bundles to form two-dimensional and three-dimensional structures.[10,11] Fibrillins are multidomain molecules with the two known domains of calcium-binding epidermal growth factor-like (cbEGF) and transforming growth factor-β-binding protein-like (TB).[12]

There are three different variants of fibrillin molecules in mammals[6,10]; fibrillin_1 (*FBN1*) and fibrillin_2 (*FBN2*), and fibrillin_3 (*FBN3*) genes that encode the human fibrillin proteins.[9,13,14] All three of them encode proteins with approximately 320–350 kDa.[6,15] The human *FBN1* gene with 66 exons is located in 15q15-21.3[15] and encodes for a proprotein named profibrillin-1.[16] Profibrillin-1 processed by the furin enzyme proteolytically in the X-Arg-X-Lys/

Arg-Arg-X consensus sequence in the exon number 65. The products of this cut (exon 1–64 and exon 65–66), respectively, are FBN1 protein which has 2704 amino acids, and asprosin protein which has 140 amino acids.[17,18] FBN1 (312 kDa) is a structural ECM glycoprotein that is the main component of 10–12 nm microfibrils and transmits the tensile strength of ECM.[4,6,18] The FBN1 has a repeated structural domain; for, example, the motif similar to the epidermal growth factor is repeated 47 times in FBN1, 43 of which have a consensus sequence for calcium binding and are called calcium binding repeats.[19] The FBN1 proteins in extracellular microfibrils create the ability to stretch in the ligaments, skin, veins, lens of the eye, nerves, and muscle tissues.[20,21] As an essential member of the microfibrils, FBN1 has a role in the formation of elastic fibers.[22–24] To assemble an elastic fiber, fibrillin microfibrils act as a scaffold for the deposition of tropoelastin.[25] Not only playing a role in ECM structure and elasticity, it also can regulate different cellular signaling pathways, including, apoptotic cell death, and proliferation. FBN1 is one of the modulators of the tissue microenvironment and plays important functions in the regulation of the growth and development of vertebrates.[26,27] It has been reported that FBN1 induces apoptosis in endothelial cells, and also prevents the proliferation of cells in vitro.[28] Both cellular adhesion and proliferation could be regulated by integrins binding to the Arg-Gly-Asp (RGD) motif located at the fourth TB domain of human FBN1, which is an accessible and flexible motif.[29] It should be mentioned that not all RGDs of the ECM are functional[30]; however, all three fibrillin proteins have RGD domains. An RGD site located at the tail of TB4 is present in all three fibrillins. In addition to this common RGD, FBN2 has an RGD in TB3, and FBN3 has an RGD in cbEGF18.[31] In addition to fibrillins, other glycoproteins, such as latent transforming growth factor-β-binding proteins (LTBPs), also can be found in the structure of the microfibrils.[8,9,13] Fibrillins are structurally related to LTBPs; these are called the fibrillin/LTBP family.[32] FBN1 and LTBP-1 also interact with each other and cause the repository of transforming growth factor β (TGF-β) in the ECM.[10,33,34] In general, TGF-β binds to LTBP through an interface called LAP, and these bonds are formed between the cysteine residues of LTBP and LAP (Figure 1).[32] Fibrillins serve as scaffolding factors to help the assembly of multiprotein complexes to help maintain tissue homeostasis.[6] They also function in tissue homeostasis through interaction with TGF-β and the bone morphogenetic proteins.[8,9,13,35] Li et al. reported in a study that FBN1 is upregulated in different chronic kidney diseases and creates a hostile microenvironment for endothelial cells. Fibrillin-rich microenvironments play an important role in driving endothelial cell damage and vascular rarefaction in CDK.[28]

Asprosin, a secreted glucogenic hormone, in mammalian cells, is a 30 kDa protein derived from the c-terminal cleavage of the profibrillin.[17,18] The source of asprosin secretion is adipose tissue.[17] In response to fasting conditions, asprosin stimulates gluconeogenesis leading to glucose secretion in the liver, and it also activates the maintenance of glucose homeostasis with the G protein-coupled receptor (olfactory receptor family 4 subfamily M member 1).[18] An increment in the serum level of asprosin has been seen in people with type 2 diabetes, insulin resistance, and women with polycystic ovary syndrome (PCOS).[17]

In general, mutations in *FBN1* and *FBN2* lead to fibrinopathies, which are disorders of connective tissue and affect tissues such as eyes, skin, heart, and skeletal tissue.[9] Missense mutations in *FBN1* lead to Marfan syndrome, an autosomal dominant connective tissue disorder.[14,27,36,37] This syndrome affects the supporting connective tissue of the joint and body organs.[38] Until today, about 1800 mutations in the *FBN1* gene that lead to Marfan syndrome have been identified. Neonatal progeroid syndrome (NPS) is also generated by a mutation in the c-terminal region of the *FBN1* gene resulting in the shortening of the 3′ ends, and ablation of asprosin in NPS patients,[18,39] which suffer from severe weight loss.[18]

The human *FBN2* gene maps to 5q23-31 and encodes a 315 kDa protein with 2912 amino acid length.[4,15] FBN2, a constituent of connective tissue microfibrils, plays a role in the initial process of elastic fiber assembly in the embryo.[40] At first, it was believed that FBN2 has insignificant expression in the postnatal period, but currently, it is determined that FBN2 forms the constructional core of microfibrils and is covered by a layer of FBN1 which means that it also has postnatal expression.[4,10] It is said that FBN2 is involved in the assembly of fibronectin around tracheal smooth muscle cells and in the formation of elastic fibers in the tracheal smooth muscle cells.[41] *FBN1* and *FBN2* are homologous at the nucleotide level, and in comparing 58% of their sequences, 84% similarity was observed between them.[15]

There are heterozygous mutations in the *FBN2* gene leading to congenital contractile arachnodactyly disease.[40,42] In fact, Congenital contractural arachnodactyly or Beals-Hecht syndrome is a hereditary connective tissue disorder with autosomal dominant inheritance related to Marfan syndrome.[15,43]

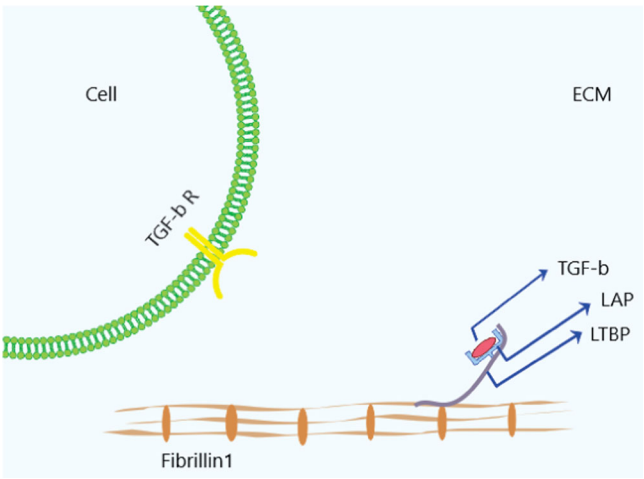

FIGURE 1 In this figure, the relationship between TGF-β and human fibrillin 1 is shown. ECM, Extracellular matrix; LAP, latency-associated propeptide; LTBP, latent transforming growth factor-β-binding proteins; TGF-β, transforming grow factor; TGF-β R, transforming grow factor receptor.

The *FBN3*, another member of the fibrillins family, is located in 19p13.3-19p13.2.[15] Unlike *FBN1* and *FBN2*, *FBN3* is not well-known, and even some studies have stated that it exists only in the complementary DNA sequence. The highest level of FBN3 expression has been observed in the fetal tissue. However, *FBN3* is observed in the microfibrils of the ECM of tissues such as kidneys, adrenal glands, skin, lungs, skeletal muscles, adult brains, stomach, ovaries, and skeletal elements that are growing.[44,45] It also seems that FBN3 participates in the pathogenesis of PCOS.[46] Studies on the lesser-known member of the fibrillins family, *FBN3*, have shown that mutations in this gene are related to Bardet–Biedl syndrome.[9] In addition, the homozygous missense variant of *FBN3* is related to Klippel–Trenaunay–Weber syndrome.[47]

Until now, the mutation of genes encoding fibrillin and its consequences had been given more attention in structural disease of connective tissues; however, considering its various functions in apoptosis modulation, TGF-β regulation, and tissue microenvironment homeostasis, attention has also been paid to the role of fibrillins in cancers. There are some reports on different human cancers illustrating the association of fibrillin with carcinoma. This review was organized with a focus on investigating the roles of the fibrillin family in cancers. Therefore, fibrillins can be considered new targets for the study of cancers in the future.

2 | FIBRILLINS AND CANCERS

Cancer progression is significantly related to the condition of the tumor microenvironment.[48] Tumor growth is specially related to the structure and function of the tumor microenvironment,[49] which includes stromal cells, endothelial cells, immune cells, fibroblasts, and ECM.[48,49] ECM has a dynamic and three-dimensional, and noncellular structure[50]; At the molecular level, ECM not only provides structural support but also supports biochemical reactions in cell, and even ECM constituents have been shown to play dominant roles in tumor development.[51] In addition to their structural roles in the ECM, microfibrils and specially FBN1 contribute to integrin-mediated signaling, proliferation, and migration, and adhesion of fibroblasts, smooth muscle cells, and endothelial cells. One of the common goals in studies is to check the expression level of genes.[52] The human fibrillin gene is also one of the genes whose role has recently been noticed in cancers.

2.1 | Lung cancer

There is evidence showing that *FBN1* contributes to the migration process of lung and mesenchymal cells.[29] Hong et al. investigated the expression of the *FBN2* gene in 97 lung cancer tissues and the effect of *FBN2* knockdown in lung cancer cell lines. They reported that the expression level of *FBN2* was associated with the patient's TNM stage and lymph node metastasis status. Also, their results showed that the permanence time of patients with high-*FBN2* expression was extremely decreased compared to patients with low-*FBN2* expression, which indicated that higher FBN2 expression is useful for lung cancer prognosis. Also, studies showed that *FBN2* knockdown significantly hindered the expansion of PC-9 and H1640 lung cancer cells with decreased clone formation ability, invasion, and migration. Moreover, in PC-9 cells, knockdown of the *FBN2* gene essentially restrained expression levels of N-cadherin and vimentin and upregulated levels of E-cadherin.[53]

In a study, Chen et al. reported that abnormal methylation of *FBN2* in 55% (6/11) of non-small cell lung cancer cell lines, but not observed in the small cell lung cancer cell lines. Also, in primary lung cancer, 49% of tumors had *FBN2* methylation, but FBN2 methylation was observed in only 7% of nonmalignant lung tissues. Moreover, *FBN2* methylation often occurs in large tumors with metastasis or advanced stages. They suggested that the methylation and silencing of *FBN2* in tumors can be related to carcinogenesis and metastasis.[54]

The outcome of this study shows that the reduction of *FBN2* expression has a function in the progression of lung cancer, but the effects of changes in the expression of *FBNs* in different cancers are contradictory, which we will mention below.

2.2 | Colorectal cancer (CRC)

Different investigations were carried out on the methylation status of the *FBN* genes in CRC patients, and they reported aberrant methylation and altered gene expression of the fibrillin genes in colorectal patients. Yi et al. observed that the *FBN2* gene promoter is hypermethylated in most CRC cell lines and primary tumors. The reduced *FBN2* gene expression, which occurs consequent to the promoter hypermethylation, can be investigated as a biomarker in the early diagnosis of CRC.[55]

In relation to further studies in the field of CRC, Hibi et al. observed that 63% of CRC patients showed *FBN2* methylation DNA in the tumor tissue. In addition, when measuring the methylation in serum DNA, only 8% of the patients have methylated *FBN2* in circulation. Further examination showed that *FBN2* methylation was found in the serum DNA of male patients and patients with liver metastasis.[56]

In addition to the studies conducted on tumor tissue samples, Guo et al. observed the methylation of the *FBN1* gene in stool samples of patients with colon cancer. Methylated *FBN1* in the stool samples was observed in 72% of patients and 7.6% of healthy groups in their stool samples. This study also suggested that hypermethylation of *FBN1* promoter is a biomarker for CRC.[57] According to the studies, the hypermethylation of *FBN1* promoter can be considered a biomarker for CRC.

2.3 | Ovarian cancer

There are some studies indicating the association of *FBNs* with tumor progression and metastasis in ovarian cancer cells. As shown by

TABLE 1 Observation and investigation of fibrillin family members in different tumor types.

Gene	Location/cell line	Observation	Intervention	Relation with tumor	References
FBN2	Lung/PC-9 and H1640 lung cancer cells	Relationship between FBN2 with migration and invasion of lung cancer	Fibrillin 2 gene Knockdown	**A.** Expression of *FBN2* was related to patient's TNM stage and lymph node metastasis **B.** Knockdown significantly hindered the expansion of PC-9 and H1640 lung cancer cells	[53]
FBN2	Non-small cell lung cancer cell lines/lung	Aberrant methylation of FBN2 in cell line and tumor		Methylation and silencing of *FBN2* in tumors can be related to metastasis	[54]
FBN2	Colorectal cancer cell lines and colorectal tumors	*FBN2* gene promoter was hypermethylated		The promoter hypermethylation of FBN2 can be investigated as a biomarker in the early diagnosis of colorectal cancer	[55]
FBN2	Colorectal cancer tumor	*FBN2* methylation DNA in the tumor tissue			[56]
FBN1	The stool samples of colorectal cancer	Methylation of *FBN1* in the stool samples of colorectal cancer patients		Hypermethylation of *FBN1* promoter is a biomarker for colorectal cancer	[57]
FBN1	Ovarian cancer cell line	Relationship between FBN1 expression and metastasis process in ovarian cancer	Silenced the expression of *FBN1*/ adding recombinant FBN1 protein	The FBN1 increases tumorigenesis and metastasis in ovarian cancer	[20]
FBN1	Pancreatic ductal adenocarcinoma (PDAC)	*FBN1* gene has a direct relationship with the level of immune cell infiltration in the tumor		The high expression level of the *FBN1* gene has a positive relationship with a poor prognosis for PDAC	[59]
FBN2	Esophageal cancer tumor	*FBN2* methylation in tumor tissue		A decline in *FBN2* gene methylation leads to an increase in its expression	[60]

Abbreviation: FBN, fibrillin.

Wang et al., *FBN1* silencing resulted in increasing the expression level of E-cadherin and β-catenin. Also, adding recombinant FBN1 protein suppressed the expression of E-cadherin and β-catenin. Overall, their results showed that FBN1 increases tumorigenesis and metastasis in ovarian cancer. Overexpression of FBN1 can be a reason for the early recurrence of ovarian cancer.[20] The research of Chen et al. shows that *FBN1*, along with three other genes, can be introduced as a marker to check the survival time of ovarian cancer patients.[58]

According to the evidence, it can be concluded that increasing the expression of *FBN1* reduces the adhesion between cells in cancer cells, but this effect of *FBN1* needs further investigation in other types of cancers as well.

2.4 | Other cancers

2.4.1 | Pancreatic ductal adenocarcinoma (PDAC)

The *FBN1* gene can contribute to immune cell infiltration in tumors. For example, Hong Luan showed that *FBN1*, along with two other genes (SPARC, COL6A3), have a direct relationship with the level of immune cell infiltration, including CD4+ T cells, CD8+ T cells, B cells, neutrophils, macrophages, and dendritic cells in the PDAC. Also, high expression levels at the *FBN1* gene showed a positive relationship with a poor prognosis for PDAC. Moreover, it was reported that *FBN1* contributes to the regulation of immune cell infiltration in the PDAC; however, more research is needed to investigate its underlying mechanism.[59]

2.4.2 | Esophageal cancer

Studies appear that the level of *FBN2* methylation in esophageal tumor tissue was higher than in tumor margin tissue. To determine whether the methylation of *FBN2* leads to an increase or decrease in its expression, Tsunoda et al. used 5-aza-2'-deoxycytidine treatment as a demethylation agent, and found a decline in *FBN2* gene methylation, leading to an increase in its expression.[60]

2.4.3 | Thyroid cancer

Changes in the level of ECM components have been observed in thyroid cancer, and evidence is reported that ECM modulation can affect thyroid cancer. For example, silencing fibronectin as one of the components of the ECM prevented the proliferation of thyroid cancer cells.[61] Considering the role of fibrillin as one of the ECM proteins, Tseleni-Balafouta et al. investigated the expression of the *FBN1* gene in normal thyroid tissue and thyroid carcinomas. Their results showed that FBN1 immunoreactivity was weak in normal thyroid tissue. But using immunohistochemistry, they identified FBN1 in the cytoplasm of neoplastic thyroid carcinoma cells. Their results confirmed previous studies and showed that fibrillin is produced by epithelial cells and fibroblastic cells.[62] The summary of the research results for the fibrillin family members in different tumor types is shown in Table 1.

3 | CONCLUSION

Fibrilin, as one of the main integrants of the ECM, can function in the tumor microenvironment affecting cellular proliferation, adhesion, metastasis, and immune cell infiltration in the tumor. Altogether various studies showed higher expression of fibrillins in different tumor tissues correlated with the patient's survival; however, there are controversial findings in this regard, as some other cancers showed hypermethylated FBN promoters with lower gene expression levels. Although studies have been conducted on fibrillin genes in tumors, the exact mechanism of how this protein acts in cancer tissue is unknown. Regarding the potential of fibrillin in cancer progression; for future studies, we suggest investigating its association with its expression level changes in other types of cancer.

AUTHOR CONTRIBUTIONS

Mahsa Mahdizadehi: Writing—original draft; writing—review and editing. **Marie Saghaeian Jazi**: Writing—review and editing. **Seyyed Mostafa Mir**: Writing—review and editing. **Seyyed Mehdi Jafari**: Supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

TRANSPARENCY STATEMENT

The lead author Seyyed Mehdi Jafari affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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