

REVIEW

Behind the scenes: how the EMILIN/Multimerin family shapes the cancer landscape

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In recent years, the tumor microenvironment has gained recognition as a key regulator of cancer progression. A central component of the tumor microenvironment, the extracellular matrix, undergoes dynamic remodeling during tumor development and plays a crucial role in disease pathogenesis. This review highlights the EMILIN/Multimerin family as a paradigm of the extracellular matrix's diverse and complex functions in cancer. Owing to their intricate domain architecture, these proteins engage in multifaceted interactions, not only directly modulating tumor cell proliferation and migration but also influencing other elements of the tumor microenvironment such as blood, lymphatic vessels, and immune cells. The functional landscape of these interactions is further complicated by proteolytic processing, which can both disrupt native functions and generate bioactive fragments with novel biological activities. Importantly, some of these fragments are detectable in biological fluids, suggesting their potential as predictive or prognostic biomarkers and contributing to the advancement of personalized therapeutic strategies.

Abbreviations

AKT, protein kinase B; BRAF, B-rapidly accelerated sarcoma; BV, blood vessel; CAF, cancer-associated fibroblast; CCN, conserved, cysteine-rich, and N-terminal domain-containing protein; ccRCC, clear cell renal carcinoma; CD, cluster of differentiation; CLEC, C-type lectin domain family member; CLL, chronic lymphocytic leukemia; CNTNAP, contactin-associated protein family member; CSF, colony-stimulating factor; CTLA, cytotoxic T-lymphocyte antigen; CTLD, C-type lectin domain; CXCR, C-X-C chemokine receptor; DISC, death-inducing signaling complex; DR, death receptor; EC, endothelial cell; ECM, extracellular matrix; EDEN, EMI-domain endowed; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; EV, extracellular vesicle; FAK, focal adhesion kinase; FREM, FRAS1-related extracellular matrix; Her, human epidermal growth factor receptor; HIV, human immunodeficiency virus; HPV, human papillomavirus; IGFBP, insulin-like growth factor binding protein; IL, interleukin; Jak, Janus kinase; LAG, lymphocyte activation gene; LGG, low-grade gliomas; LN, lymph node; LRP, low-density lipoprotein receptor-related protein; LV, lymphatic vessel; MDSC, myeloid-derived suppressor cell; MMP, metalloproteinase; NET, neutrophil extracellular trap; PD, programmed cell death protein; PDGF-, platelet-derived growth factor; PI3K, phosphoinositide 3-kinase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCC, squamous cell carcinoma; SNX27, Sorting Nexin 27; STAT, signal transducer and activator of transcription; STIC, serous tubal intraepithelial carcinoma; STIL, serous tubal intraepithelial lesion; TGF, transforming growth factor; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TLR, toll-like receptor; TME, tumor microenvironment; TRAIL, TNF-related apoptosis-inducing ligand; TSPAN, tetraspanin; UTR, untranslated region; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; YAP, yes-associated protein.

Introduction

Cancer is one of the leading causes of death worldwide and represents a significant burden on health systems. It is a heterogeneous disease arising from a series of genetic mutations accumulating in tumor cells, leading to uncontrolled cell growth, invasion, and eventually, metastasis.

While genetic alterations are essential for cancer initiation, tumor progression is strongly influenced by the tumor microenvironment (TME) [1]. The TME is a multifaceted network composed of cellular and noncellular components, which, thanks to dynamic interactions, exert profound effects on cancer cells [2]. These components comprise immune cells, endothelial cells (ECs), cancer-associated fibroblasts (CAFs), and extracellular matrix (ECM), all of which aid tumor progression, impinging on key processes such as the immune response, angiogenesis, and metastasis [3].

One of the TME components that has attracted mounting interest is the ECM [4]. The ECM is a sophisticated, three-dimensional network composed of proteins, glycoproteins, proteoglycans, and hyaluronan. In normal tissues, it maintains tissue homeostasis, providing structural support and facilitating biochemical signaling, thus regulating cell adhesion, migration, and differentiation [5,6].

In cancer, however, the ECM undergoes extensive remodeling. Certain components, including collagen, fibronectin, and hyaluronan, are aberrantly overproduced, leading to the formation of a denser and stiffer matrix that supports cancer cell survival, migration, and invasion [6–8]. Furthermore, the fibrotic tissue arising from excessive ECM deposition can hinder the effectiveness of the therapeutic agents by limiting penetration into the tumor core [9,10]. On the contrary, the expression of other ECM molecules is reduced or subjected to proteolytic cleavage by enzymes such as metalloproteinases (MMPs) and other proteases [11]. These degradation processes generate bioactive ECM fragments that often acquire novel functions, facilitating tumor progression [6,12], and creating new routes for cancer cells to colonize distant organs [11,13]. As a result, these profound modifications can create a permissive environment that fosters tumor development and progression [6,7,14,15].

The ECM does not only directly influence the behavior of cancer cells but also impinges on other TME components, establishing intricate crosstalks that ultimately shape the tumor fate. Indeed, one of the first endogenous anti-angiogenic molecules to be discovered was the ECM protein endostatin, a C-terminal fragment of collagen XVIII [16]. Angiogenesis, the

formation of new blood vessels (BVs) from pre-existing vasculature, is essential for tumor growth as it ensures a continuous supply of oxygen and nutrients. For this reason, it has long been viewed as a promising therapy target [17,18], with anti-angiogenic approaches now approved for cancer treatment [19,20]. Besides endostatin, numerous ECM molecules were subsequently demonstrated to regulate angiogenesis [21,22], adding further complexity to this process. Additionally, the ECM serves as a reservoir of angiogenesis-active growth factors that are released upon remodeling [23], thereby influencing vascular development in the tumor context.

The ECM also affects lymphangiogenesis [5,24,25], the formation of lymphatic vessels (LVs), which plays a key role during the latest stages of tumor progression, facilitating the dissemination of cancer cells to regional lymph nodes (LNs) and distant organs [26,27]. On the other hand, in concert with the ECM, the lymphatic system also regulates the immune response [28]. While LVs and BVs provide the physical routes for cell trafficking, the ECM influences the immune landscape of the tumors, functioning as a scaffold for immune cell infiltration and modulating their activation through the presentation of growth factors and cytokines [29,30]. Moreover, the ECM can also contribute to the establishment of an immunosuppressive environment, and its targeting has emerged as a promising strategy to overcome immune evasion and improve immunotherapy efficacy [14]. A deeper understanding of the intricate interplay between the ECM and its remodeling, angiogenesis, lymphangiogenesis, and inflammation is therefore essential to identify new therapeutic strategies and improve patients' survival.

In this review, we will focus on the EMILIN/Multimerin protein family, a group of heterogeneous, widely distributed ECM molecules, characterized by the presence of the cysteine-rich EMI domain at the N terminus [31].

The EMILIN/Multimerin family: Protein architecture and localization patterns

The EMILIN/Multimerin family, also known as EMI domain endowed (EDEN) family [32,33], consists of seven genes characterized by the presence of the EMI domain (~80 amino acid residues) at the N terminus (Fig. 1). It comprises five large glycoproteins, EMILIN-1, EMILIN-2, EMILIN-3, Multimerin-1, and Multimerin-2, where the EMI domain is followed by a long α -helical coiled-coil region, and, except for

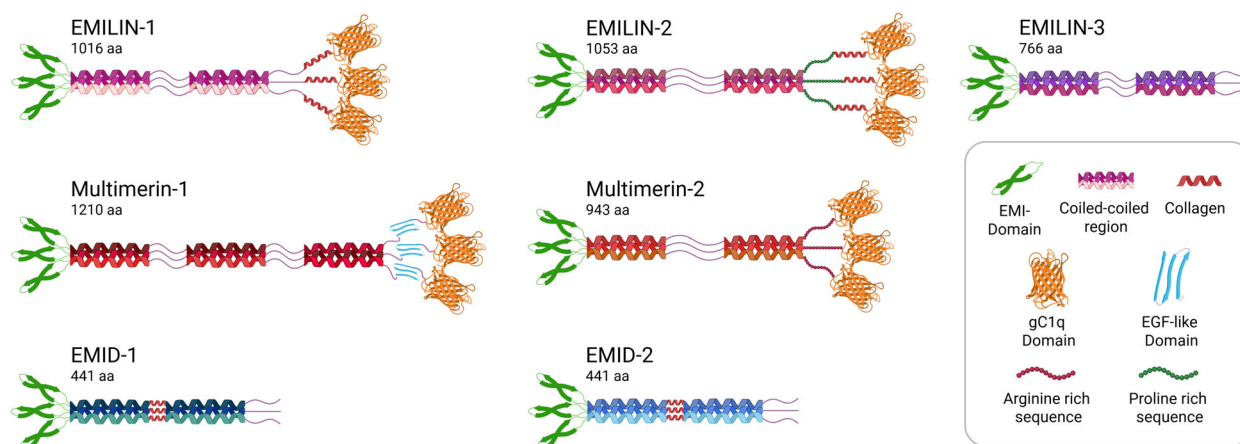


Fig. 1. Domain architecture and structural features of the EMILIN/Multimerin (EDEN) protein family. Schematic representation of the structure of the EMILIN/Multimerin (EDEN) family, which comprises seven glycoproteins with an N-terminal EMI domain (~80 residues). Five members (EMILIN-1, EMILIN-2, EMILIN-3, Multimerin-1, and Multimerin-2) feature an EMI domain, α -helical coiled-coil region, and (except EMILIN-3) a C-terminal gC1q domain. EMID1 and EMID2 share only the presence of the EMI domain and collagen stretches. The EMI domain contains seven conserved cysteines forming three disulfide bonds, facilitating protein interactions and O-fucosylation. As indicated, many of the members contain unique motifs at the end of the coiled-coil region, prior to the collagen stalk, when present. All members likely form homotrimers, though experimentally confirmed only for EMILIN-1 and EMILIN-3. The putative secondary structures of each domain have been represented based on the modeling available at the AlphaFold Protein Structure Database (<https://alphafold.ebi.ac.uk/>). Created with [BioRender.com](https://www.biorender.com/).

EMILIN-3, a C-terminal globular gC1q domain. The two other members, EMID1 and EMID2 (also known as Emu1 and Emu2), contain only the EMI domain and share two collagen stretches and a conserved C-terminal domain, while they lack structural similarities to other EDEN members [34].

The EMI domain contains seven conserved cysteines forming three disulfide bonds [31], and, in concert with the gC1q domain, it mediates protein–protein interactions and multimerization, and can be O-fucosylated [35]. In fact, all EDEN family members are predicted to form homotrimers despite this being experimentally proven only for EMILIN-1 and EMILIN-3 [36,37]. However, the role of the gC1q domain in homotrimerization seems to be dispensable, since multimerization occurs also in members lacking this domain, possibly through the EMI domain and collagenic sequences. Both EMILIN-1 and EMILIN-2 feature a short collagen-like Gly-X-Y repeat, though EMILIN-1 forms a weak triple helix while EMILIN-2 remains less structured due to reduced glycine content. Notably, EMILIN-1 contains a leucine zipper domain preceding its collagen stalk, contrasting with EMILIN-2's proline-rich sequence in the same region. Multimerin-1 differs from Multimerin-2 by possessing an RGD cell-attachment motif and a calcium-binding EGF-like repeat, whereas Multimerin-2 lacks RGD but carries an arginine-rich sequence. EMILIN-3 is structurally

truncated, terminating after the leucine zipper/collagen region without a gC1q domain. The gC1q domains typically adopt a jelly-roll β -sandwich fold, though EMILIN-1 uniquely has only nine β -strands with acidic loops that bind integrin $\alpha 4 \beta 1$ via a critical glutamic acid motif [32,38].

Regarding the localization and tissue distribution, EMILINs are classical ECM proteins primarily localized to elastic fiber systems and are expressed during embryonic development [39]. EMILIN-1 and EMILIN-2 are found in elastic and oxytalan fibers, particularly in skin, large BVs, and lungs, where they localize at elastin-fibrillin interfaces [40,41]. EMILIN-1 is also crucial in the lymphatic vasculature, with high expression in lymphatic valve leaflets and anchoring filaments [42,43]. EMILIN-1 and EMILIN-2 are highly expressed in the lamina propria adjacent to the gastric islands [44,45]. EMILIN-2 is also deposited in the skin [46,47], and by different cell types, including fibroblasts, astrocytes, and smooth muscle cells; it shows perivascular dermal distribution and increases in scleroderma/fibrosis models [48,49]. In cardiovascular development, EMILIN-2 is critical for heart/vessel formation and platelet aggregation [50–53]. Finally, EMILIN-2 is also expressed in the cochlea, where it plays a critical function [54–56].

Originally termed EMILIN-5, EMILIN-3 expression was detected at the E8.5–E9.5 stage of embryogenesis

in the tail bud region, a structure known to contain a multipotent stem cell population [37]. However, limited data exist on EMILIN-3 expression and distribution. It is expressed by mesenchymal cells during osteogenesis and in developing limb perichondrium but, unlike other EMILINs, not in the cardiovascular system [37]. Multimerins, instead, exhibit a more cell-specific distribution. Multimerin-1 is usually retained in the secretion granules of megakaryocytes and platelets, where it is complexed with coagulation factor V, and ECs [57–61]. Multimerin-2, initially identified as EndoGlyx-1 in a screen for EC surface markers [62], was later cloned and characterized and is specifically expressed by ECs [63]. Its structural similarity to Multimerin-1 suggests shared ancestry, likely arising from gene duplication [64]. EMID1 and EMID2 are structurally different from the other members of the family, and their expression in adult tissues remains poorly characterized. EMID1 is upregulated during kidney development [34], whereas EMID2 is present in the upper and lower airways [65].

Interestingly, the members of this family are involved in a wide range of biological processes that are central to cancer biology, including tumor cell behavior, angiogenesis, lymphangiogenesis, and the immune response. Importantly, during tumor progression, the function of the EMILIN/Multimerin family can be compromised by the action of proteases, overall promoting malignancy. This review will summarize current knowledge regarding the role of these proteins, emphasizing their profound impact on the TME and tumor progression. We will highlight their emerging potential as molecular targets and/or predictive biomarkers in cancer.

The EMILIN/Multimerin family: Natural brakes on tumor growth and metastasis

Numerous studies indicate that the ECM generally promotes tumor progression, with its components and corresponding receptors actively favoring cancer cell growth and spreading. Indeed, integrin, which primarily regulates ECM signaling, is a well-established positive regulator of cell growth [66]. However, only a limited number of ECM proteins, such as decorin [67], perlecan [68,69], and some members of the CCN family of matricellular proteins [70] are known to exert primarily a tumor-suppressive function.

The realm of the EMILIN/Multimerin family is peculiar in this perspective since most of the molecules are known to directly or indirectly restrain the growth and progression of tumors. In this section, we will

summarize the current knowledge on the role of these molecules in directly affecting cancer cell behavior (Fig. 2).

The glycoprotein EMILIN-1 was initially identified for its role in maintaining blood pressure through regulation of the TGF- β signaling pathway [71]. Subsequent studies have broadened its functional profile, linking it to the control of cell proliferation and migration. Collectively, most of the studies have shown that EMILIN-1 exerts antiproliferative effects, supporting its classification as a tumor suppressor in various cancers. The gC1q domain of EMILIN-1 engages integrins $\alpha 4\beta 1$ and $\alpha 9\beta 1$, modulating the adhesion and migration of different cell types [43,72–74]. Also, the antiproliferative effect of EMILIN-1 primarily hinges on the engagement of integrins. This was first observed in *Emilin1*^{−/−} mice, which showed epidermal thickening and a higher number of Ki67-positive cells in both the epidermis and dermis compared to wild-type counterparts [43]. The underlying mechanism involves PTEN, which mediates the crosstalk between integrins $\alpha 4\beta 1/\alpha 9\beta 1$ and the TGF- β signaling pathway, leading to the downregulation of proliferative cues through ERK inhibition [43]. Similar altered proliferative signals were observed in the context of lymphatic valves [75]. Notably, *Emilin1*^{−/−} mice developed larger lymphangiomas [42], and exhibited accelerated tumor growth with increased tumor size and number in a model of skin carcinogenesis [76]. Similarly, in a HER2-driven breast cancer model, $\Delta 16\text{HER2}/v\text{Emilin1}^{−/−}$ mice showed premature tumor onset and increased number of tumor foci [77]. EMILIN-1's protective role was also evident in colon carcinogenesis, where, through an integrin-dependent mechanism, its absence led to higher adenoma development [78]. Indeed, in colon cancer cell integrin $\alpha 4\beta 1$ engagement by EMILIN-1 induces H-Ras ubiquitination and degradation, suppressing pERK1/2 and proliferation [79]. This mechanism, conserved across different tumor models, reveals EMILIN-1's unique ability to mediate antiproliferative signaling through $\alpha 4\beta 1$ and $\alpha 9\beta 1$ integrins, a feature distinguishing it from other ligands [80–83]. Conversely, in chronic lymphocytic leukemia (CLL), the EMILIN-1- $\alpha 4\beta 1$ interaction promotes pro-survival signals [84], suggesting that EMILIN-1's effects are context-dependent and influenced by the TME. In gastric and head and neck squamous cell carcinoma, EMILIN-1 suppresses cancer cell proliferation and invasion via the TSPAN9 transmembrane protein and the modulation of ERK1/2 and MMP9 [85,86]. Additionally, in liver cancer, ARID1 promotes EMILIN-1 expression, thereby inhibiting cell migration and invasion [87]. Similarly, in colorectal cancer,

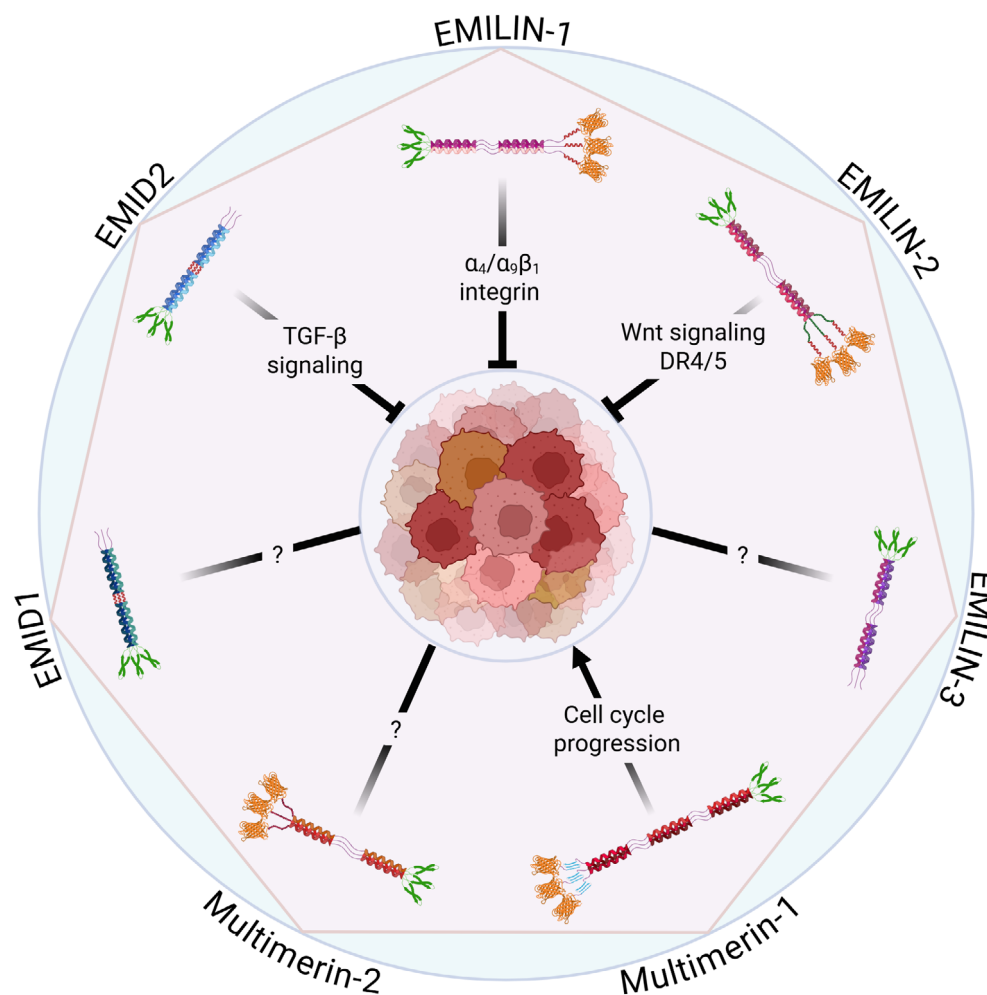


Fig. 2. The EMILIN/Multimerin family members modulate cancer cell behavior through receptor-mediated signaling. The EMILIN/Multimerin family predominantly exerts tumor-suppressive effects on cancer cells: EMILIN-1 inhibits proliferation by engaging integrins $\alpha_4\beta_1$ and $\alpha_9\beta_1$, while EMILIN-2 suppresses Wnt signaling through ligand sequestration and triggers apoptosis via death receptor (DR4/DR5) binding. EMID2 attenuates tumor growth through modulation of TGF- β signaling. In contrast, Multimerin-1 uniquely promotes cell cycle progression, though the underlying molecular mechanism remains uncharacterized. The direct effects of EMILIN-3, Multimerin-2, and EMID1 on tumor cell behavior remain to be experimentally established. Created with [BioRender.com](https://www.biorender.com).

RORB-driven upregulation of EMILIN-1 has been found to suppress metastasis [88].

EMILIN-1 mutations in humans are rare and are associated with connective tissue disorders and neuropathies [89,90]. In tumors, where matrix remodeling is a hallmark, the loss of EMILIN-1 function is likely due to proteolytic degradation, rather than gene mutation. In fact, proteases, such as neutrophil elastase, secreted by tumor-associated inflammatory cells, contribute to its degradation, affecting cancer progression [91–95]. EMILIN-1 has been shown to colocalize with neutrophil extracellular traps (NETs), structures made of processed chromatin bound to granular elastase and myeloperoxidase [96], favoring its degradation

and impairing its suppressive function [97]. This cleavage occurs within the gC1q domain, which, by contrast, is resistant to the action of other matrix proteases such as MMP14, MMP3, and MMP9, collagenase, and proteinase-3 [91]. Additionally, EMILIN-1 fragments have been found in small extracellular vesicles (sEVs) and associate with melanoma and colon cancer progression [98,99]. Moreover, in breast cancer, elevated levels of EMILIN-1-derived peptides were identified in liquid biopsies via LC-ESI-MS/MS spectrometry [100], although the clinical significance of this finding remains elusive.

EMILIN-1 expression can also be downregulated by promoter hypermethylation, as seen in rhabdomyosarcoma

and uterine carcinosarcoma [101,102]. EMILIN-1 has emerged as a predictive/prognostic biomarker in several types of cancers. Elevated EMILIN-1 levels have been correlated with reduced proliferation rates in non-small-cell lung cancer [103], and improved therapeutic response in breast cancer [104]. Conversely, elevated EMILIN-1 levels are observed in osteosarcoma, Ewing's sarcoma, and ovarian carcinoma [105–107]. The dual role of EMILIN-1 as both a tumor suppressor and, in some cases, a marker of poor prognosis [108–113], underscores the complexity of its function, which appears to be highly context-dependent and influenced by the TME. Further studies are required to validate these contrasting observations and to evaluate the structural and functional integrity of EMILIN-1 across different tumor settings.

EMILIN-2 exhibits tumor-suppressive activity through multiple mechanisms. Studies performed in a sarcoma tumor model demonstrate that it functions as a negative regulator of cancer cell proliferation and can induce apoptosis through the interaction with TRAIL death receptors DR4 and DR5 [114,115]. Specifically, a 90-amino acid residues sequence of the N-terminal coiled-coil region binds to DR4, leading to formation of the death-inducing signaling complex (DISC) and subsequent activation of caspase-8 [116]. Importantly, this apoptotic effect shows selective toxicity toward tumor cells, while leaving normal cells unharmed [116].

In breast cancer, EMILIN-2 inhibits cell proliferation by suppressing Wnt signaling. The EMI domain of EMILIN-2 directly binds Wnt1, competes with the Frizzled receptor and reduces LRP6 phosphorylation. This leads to downregulation of β -catenin, TAZ, and their target genes (e.g., *c-Myc*, *cyclin D*), decreasing S-phase entry and phospho-histone H3-positive cells [117], overall diminishing breast cancer cell tumorigenicity. Accordingly, ectopic expression of EMILIN-2 *in vivo* suppressed Wnt signaling, tumor growth, and metastasis. In support of these findings, an *in silico* meta-analysis of 2878 breast cancer patients revealed an inverse correlation between EMILIN-2 and Wnt target genes, with high EMILIN-2 expression associated with improved relapse-free survival [117]. The EMILIN-2-Wnt interaction may also be relevant in HPV-E6-driven cervical and other anogenital cancers. Indeed, the oncogenic HPV-E6 through the interaction with the endosomal protein SNX27, impairs EMILIN-2 trafficking and deposition, thereby weakening Wnt signaling and favoring cell proliferation [118].

In ovarian cancer EMILIN-2 emerges as a dual-function p53 effector that simultaneously regulates proliferation and metabolism [119,120]. Ovarian cancer arises from serous tubal intraepithelial lesions (STIL) to

serous tubal intraepithelial carcinoma (STIC) and eventually established tumor also modulating p53. During tumor progression EMILIN-2 is detectable in STIL and absent in STIC. Mechanistically, p53 directly activates EMILIN-2 transcription and its upregulation antagonizes tumor growth and reprograms metabolism by reducing glycolysis and promoting oxidative phosphorylation [119]. These results demonstrate that EMILIN-2 may inhibit tumor growth engaging different suppressive mechanisms in cancer cells.

In accordance with its tumor-suppressive function, EMILIN-2 is frequently downregulated through promoter hypermethylation in multiple cancers. HBV-related hepatocellular carcinoma exhibits tumor-specific EMILIN-2 hypermethylation, compared to adjacent tissue [121]. In breast cancer, it ranks among the top five methylated genes, with methylation correlating with poor prognosis, lymph node metastasis, and hormone receptor-positive status [122]. Lung adenocarcinoma shows smoking-associated EMILIN-2 methylation linked to disease progression and poor overall survival [123]. Also colorectal tumors exhibit EMILIN-2 methylation in 33% of carcinomas and 32% of adenomas, and this associates with BRAF mutations, lymphatic invasion, and metastasis [124]. In ovarian cancer, EMILIN-2 is downregulated via promoter hypermethylation, correlating with worse prognosis, while serving as a potential serum biomarker [120,125]. In melanoma, EMILIN-2 hypomethylation correlates with better outcomes [126].

The function of EMILIN-2 in the TME can be also suppressed by degradation even though the responsible enzymes have not been identified. Elevated levels of EMILIN-2 were detected in the blood serum of patients with esophageal diseases, including high-grade dysplasia and esophageal adenocarcinoma, compared to disease-free controls [127]. In gastric carcinomas, EMILIN-2 is lost across all tumor stages, further suggesting its tumor-suppressive role [44]. Notably, this suppression occurs independently of disease progression parameters. Intriguingly, when present, EMILIN-2 expression shows a significant positive correlation with increased microvascular density, as evidenced by CD31 staining patterns [44]. This vascular association suggests potential roles in tumor angiogenesis regulation beyond its direct tumor-suppressive functions, as detailed in the next section.

Intriguingly, rare EMILIN-2-PDGFB fusions in dermatofibrosarcoma protuberans mimic COL1A1-PDGFB-driven pathogenesis through PDGFRB activation, whereas, in breast cancer, this fusion associates with aggressive features, including fibrosarcomatous transformation and deep invasion [128–130].

In contrast with its downregulation in most tumors, EMILIN-2 is upregulated in cholangiocarcinoma, colon adenocarcinoma, clear cell renal carcinoma (ccRCC), esophageal squamous cell carcinoma (SCC), and low-grade gliomas (LGGs). Its expression holds a prognostic value in adrenocortical carcinoma, ccRCC, gliomas, testicular germ cell tumors, and uveal melanoma [131–133]. These contrasting results suggest that the effect of EMILIN-2 may be context-dependent. However, it must be taken into account that, while mRNA analysis reveals transcriptional activity, EMILIN-2 protein levels may not correlate due to extensive post-transcriptional regulation and ECM remodeling in tumors. This discrepancy necessitates direct protein validation through immunohistochemistry or proteomic analysis to accurately assess EMILIN-2's functional presence and clinical relevance in these cancer tissues.

The role of EMILIN-3 in directly modulating cancer cell behavior is poorly characterized. Nonetheless, EMILIN-3 expression is upregulated in low-grade gliomas (LGG) where it associates with increased tumor grade and worse prognosis [111,134], thus functioning as a potential predictive marker in this type of tumor [135,136]. In colorectal cancer, frequent copy number gains of 20q12 chromosomal regions comprising the *EMILIN-3* gene were observed [137], and the gene was also found in a signature associated with brain but not liver metastasis [138]. In addition, EMILIN-3 expression may also affect drug resistance in cancer cells [139]. However, these studies rely solely on database analyses of mRNA expression and provide no information on actual protein levels, processing, or the underlying molecular mechanisms.

Although Multimerin-1 has been primarily characterized in platelet biology [140], its direct role in cancer has not been thoroughly evaluated. Given the well-established contribution of platelets to tumor progression [141], Multimerin-1 may play a significant role in oncogenic processes. Indeed, the calcium-binding EGF-like domain of Multimerin-1 may facilitate protein–protein interactions and regulate cell proliferation, differentiation, and cancer progression [142,143]. In accordance with its role in tumors, Multimerin-1 exhibits cancer-specific expression patterns [144], being downregulated in oropharyngeal squamous cell carcinomas [145], and hepatocellular carcinoma [146], whereas it is upregulated in acute myeloid leukemia [147], pancreatic cancer [148], and cervical cancer [149]. In ovarian cancer, Multimerin-1 silencing impairs viability, migration, and invasion while increasing apoptosis and disrupting DNA repair pathways [150]. In small-cell lung cancer, its downregulation associates

with an increased sensitivity to cisplatin [151]. Interestingly, Multimerin-1 fragments have been detected in the body fluids, highlighting its diagnostic potential [149,152–154].

As an EC-specific protein, Multimerin-2 shows dysregulation in multiple angiogenesis-related diseases, including myocardial infarction [155], pulmonary hypertension [156], uveitis [157], SARS-CoV-2 infection [158], neurodegenerative diseases such as Parkinson [159], and HIV-associated infections [160]. The potential role of Multimerin-2 in cancer is underscored by its distinct dysregulation patterns across multiple tumor types, suggesting a possible involvement in tumorigenic processes. In fact, bioinformatic studies show generally reduced Multimerin-2 mRNA levels in most tumors except certain hematological malignancies and glioblastomas, where its overexpression correlates with poorer survival [111]. In ccRCC, high Multimerin-2 expression correlates with improved outcomes [161], whereas when mutated in lung adenocarcinoma associates with worse prognosis [162]. However, these gene expression analyses may not be representative of the actual protein levels in the tissues, which are substantially influenced by protease activity, as our published and preliminary data indicate. In fact, the discontinuous Multimerin-2 deposition in gastrointestinal cancers likely results from MMP2/9-mediated cleavage [22,163–165]. Proteomic analyses reveal a cancer-specific enrichment of Multimerin-2 fragments in the body fluids of ovarian [166], lung [167], breast [168], and thyroid cancer patients [169]. Interestingly, recent findings suggest a potential vascular mimicry mechanism in breast cancer through CD93/ β 1-integrin/PI3K signaling [170], though clinical validation remains needed. These collective findings position Multimerin-2 as a multifaceted potential biomarker while highlighting the need to better understand its proteolytic processing and context-dependent functions across cancer types.

Although the role of EMID proteins in cancer remains poorly understood, EMID1 has emerged as a key regulator in breast and prostate malignancies. Initially identified in highly metastatic murine mammary tumors, EMID1 was upregulated in cells with increased metastatic potential [171]. The knockdown of EMID1 in metastatic breast cancer cells reduced proliferation by delaying cell cycle progression, while promoting cell motility [171]. High EMID1, combined with low Contactin-Associated Protein Family Member 3 (CNTNAP3) and FRAS1-Related Extracellular Matrix 1 (FREM1) levels, correlates with improved breast cancer patient survival [172]. However, in lung adenocarcinoma, low EMID1 levels correlate with

poorer outcomes, hinting at context-dependent effects [173]. EMID1 is also upregulated in prostate cancer bone metastases, particularly osteoblastic lesions [174]. Thus, the role of EMID1 in affecting cancer progression and the mechanisms involved remains elusive and requires additional investigations.

Also the role of EMID2 in cancer has not been extensively investigated. Nonetheless, in a recent study, EMID2 was shown to exhibit tumor-suppressive properties, inhibiting proliferation, migration, and invasion. In fact, EMID2 emerged in a large-scale screening of secreted proteins as a potent suppressor of tumor dissemination in lung and pancreatic models [175]. Mechanistically, EMID2 blocks TGF- β maturation, preventing CAF activation and resulting in reduced YAP nuclear localization and decreased ECM stiffness, collectively suppressing invasiveness. EMID2-overexpressing tumors *in vivo* were smaller and more circumscribed, correlating with improved patient outcomes, thus highlighting its prognostic potential [175]. Whether EMID1 and EMID2 expression is regulated by proteolytic processing remains to be investigated.

Multifaceted tumor control: How EMILIN/Multimerin proteins orchestrate angiogenic, lymphangiogenic, and immunomodulatory networks in cancer

Among the EMILIN/Multimerin protein family, EMILIN-1 is the only component known to play a crucial role in the lymphangiogenesis process. In fact, EMILIN-1 is essential to maintain the integrity of LVs. EMILIN-1 deficiency results in a significant reduction in anchoring filaments, hyperplasia, enlargement, and in an irregular pattern of superficial and visceral LVs leading to mild lymphedema, impaired lymph drainage and enhanced leakage [42]. These effects are integrin $\alpha 4\beta 1/\alpha 9\beta 1$ -dependent in coordination with the VEGFR3, ultimately activating the AKT and ERK pathways [43,91,176].

In a lymphedema mouse model, EMILIN-1 degradation by neutrophil elastase weakens lymphatic EC junctions, worsening lymphedema, which can be reabsorbed using a neutrophil elastase inhibitor, suggesting a possible therapeutic approach [92]. These lymphatic alterations also have implications for cancer metastasis. In syngenic models of melanoma and lung cancer, *Emilin-1*^{-/-} animals display more LN metastasis compared to *wild-type* controls [76], likely due to compromised structural integrity of LVs. LVs are key in resolving inflammation [177], accordingly, in gastric

cancer, EMILIN-1 loss associates with chronic inflammation, impaired inflammatory cell clearance, particularly of monocytes and macrophages, and enhanced malignancy [45,78,178]. This is likely due to a combination of defective lymphatic clearance and altered expression of inflammatory mediators [45]. EMILIN-1 loss may indeed impact TGF- β signaling, influencing also macrophage polarization and immune suppression, thereby further skewing the immune balance toward a chronic inflammatory state [178]. Using single-cell RNA sequencing and a spatial transcriptomic approach, EMILIN-1 was found enriched in the tumor area characterized by high cytotoxic CD8⁺ T-cell infiltration, in a TGF- β -dependent manner [179].

However, in other contexts, high EMILIN-1 expression has been associated with resistance to radiotherapy [180], potentially due to complex interactions within the ECM and modulation of the immune microenvironment. Further studies are required to better elucidate the crosstalk between EMILIN-1 and the inflammatory microenvironment.

Beyond its direct effects on cancer cell growth, EMILIN-2 also significantly influences the TME. In fact, EMILIN-2-overexpressing tumors displayed enhanced vascularization [116]. Subsequent studies demonstrated that EMILIN-2 promotes angiogenesis by binding EGFR on ECs, activating the Jak2-STAT3 pathway ultimately promoting IL-8 expression [48]. A similar mechanism also occurs in cancer cells and fibroblasts, where the increased IL-8 production further drives EC proliferation and migration via CXCR1 [48]. In gastric cancer, EMILIN-2 expression positively correlates with CD31, used as a BV marker [44], and the increased vascularization of the tumors partly relied on increased expression of IGFBP2, SERPINE1, and VEGFA [44].

The clinical significance of these findings is underscored by observations that tumors with low EMILIN-2 expression frequently develop dysfunctional vasculature negatively impacting on treatment efficacy [48]. In fact, EMILIN-2 enhances vascular stability through different mechanisms: (1) It promotes pericyte recruitment through PDGF-BB and HB-EGF; (2) it facilitates pericyte adhesion via integrins $\alpha 5\beta 1$ and $\alpha 6\beta 1$; (3) it strengthens EC-pericyte connection by upregulating N-cadherin and collagen IV expression [181]. Importantly, the treatment with a pericyte-recruiting agent improves chemotherapy efficacy by restoring vascular functionality [181]. Particularly noteworthy is the dramatic near-complete tumor regression achieved in sarcoma mouse models through combination therapy using bevacizumab with EMILIN-2 fragments, an effect mediated by enhanced vascular

normalization and perfusion [116]. Collectively, these findings establish EMILIN-2 as a promising therapeutic target capable of simultaneously improving vascular stability and enhancing the efficacy of both anti-angiogenic agents and conventional chemotherapy.

EMILIN-2 is expressed in the bone marrow [182], and indeed, it has emerged in immune-related conditions including Kawasaki disease [183], viral infection [158], and age-related metabolic changes [184]. In cancer, EMILIN-2-challenged gastric tumor cells upregulate the expression of several cytokines, including IL-8, a cytokine involved in both angiogenesis and immune cell recruitment [44]. In ccRCC, high EMILIN-2 expression correlates with immune checkpoint upregulation (CTLA-4, PD-1, LAG3, and TIGIT), enriched T-cell infiltration, and poor prognosis [131]. In preclinical settings, EMILIN-2 deficiency correlates with increased PD-L1 expression and enhanced immunotherapy response, which led to vascular normalization and decreased hypoxia [126]. In CRC, EMILIN-2 exhibits stage-dependent immunomodulation: Early lesions from *Emilin-2*^{-/-} mice show myeloid derived suppressor cells (MDSCs) recruitment via G-CSF, while advanced tumors display unbalanced M2-polarized macrophages through a TLR-4-dependent mechanism, with low EMILIN-2 expression predicting poor outcomes [124]. In gliomas, blood–brain barrier disruption enables infiltration of peripheral monocytes/macrophages. In this context, EMILIN-2 emerged as a discriminator between peripheral macrophages and resident microglia, the brain's predominant macrophage population [185]. Comprehensive *in silico* immune profiling further revealed EMILIN-2's critical role in shaping immune cell infiltration in LGG [133]. Furthermore, breast cancer spatial analysis revealed EMILIN-2 as a key prognostic marker, with high expression in tumor (PanCK+) regions predicting poorer survival compared to immune (CD45+) regions [186]. More recently, EMILIN-2 was discovered as a target for anti-angiogenic immunotherapy. In mouse melanoma models, EMILIN-2 vaccination shrank tumors, reduced BVs, and changed immune cell activity [187]. Taken together, these findings position EMILIN-2 as a key molecule between angiogenesis and immunity, highlighting its potential as both prognostic biomarker and therapeutic target across multiple cancer types.

Studies linking EMILIN-3 to tumors are limited. However, published evidence suggests that EMILIN-3 influences the microenvironment with potential contributions during tumor progression. For instance, like other family members, EMILIN-3 inhibits the maturation of TGF- β [37], whose role in tumor-related

inflammation is well-established [188]. Additionally, EMILIN-3 interacts with heparin through its EMI domain, suggesting a potential role in modulating heparan sulfate proteoglycan-associated signaling pathways, including those mediated by Wnt, Hedgehog, and BMP ligands [37,189,190]. While these functions were characterized in developmental and cutaneous contexts, these findings raise the possibility that EMILIN-3 may indirectly influence tumor progression through modulation of the immune TME.

While Multimerin-1 is well-characterized in platelet biology and hemostasis, its potential influence on the TME remains poorly understood. Multimerin-1 may play a significant role in angiogenesis, as peptides derived from its EGF-like domain have been shown to stimulate proliferation in both keratinocytes and ECs [191]. Additionally, Multimerin-1 may also activate TGF- β under shear stress, suggesting broader vascular and immune functions [192]. The angiogenic potential, combined with Multimerin-1's established roles in vascular biology and cell adhesion, positions this molecule as a potential modulator of BV formation in both physiological and pathological contexts. Nonetheless, given the differential expression in various cancers, its involvement in cell adhesion, and modulation of signaling pathways [193,194], Multimerin-1 could play a context-dependent role in shaping the TME, representing an important area for future research.

Multimerin-2 primarily influences tumor progression by modulating the TME, particularly through the regulation of tumor-associated vasculature. When ectopically overexpressed in the TME, Multimerin-2 inhibits tumor growth by impairing vascularization, thereby restricting blood supply [195]. This angiostatic function is mediated by its ability to sequester VEGFA via its glycosylated coiled-coil domain, thereby suppressing VEGFR2 activation [195,196]. Mechanistically, Multimerin-2 reduces phosphorylation of VEGFR2 at residues Y1214 and Y1175, as well as downstream signaling through FAK and p38, ultimately inhibiting EC migration and sprouting angiogenesis [195]. Multimerin-2 expression is tightly regulated during active angiogenesis. Pro-angiogenic cytokines suppress Multimerin-2 mRNA levels, while its proteolytic degradation, primarily by MMP9 and, to a lesser extent, MMP2, further reduces its extracellular deposition [163]. Beyond angiogenesis inhibition, Multimerin-2 is crucial for maintaining endothelial junction integrity. In Multimerin-2-deficient ECs, VE-cadherin lining becomes discontinuous due to elevated VEGFR2-Y951 phosphorylation, which promotes VE-cadherin internalization [197]. Consistent with this, *Multimerin-2*^{-/-} mice exhibit defective tumor vasculature, increased

hypoxia, and impaired drug delivery, reducing therapeutic efficacy [197].

In addition to the indirect VEGFR2 modulation, Multimerin-2 directly interacts with C-type lectin domain (CTLD) family receptors, including thrombomodulin, CLEC14A, CD93, and CD248 [198]. These interactions fine-tune angiogenic processes and influence broader TME dynamics [199–201]. Buried among other data of a 2012 proteomic screen [202], the Multimerin-2-CLEC14A interaction waited several years before its mechanistic importance in angiogenesis was revealed. In two consecutive studies, Multimerin-2 was demonstrated to bind to CLEC14A via the CTLD domain and to CD93 via the F238 residue, and disruption of this interaction suppresses sprouting angiogenesis and tumor growth [203–207]. In glioblastoma, Multimerin-2 colocalizes with CD93-positive vessels, stabilizing CD93- β 1-integrin interactions and promoting actin cytoskeleton remodeling, EC adhesion, and migration [208,209]. This complex also guides fibronectin fibrillogenesis, as tumors from *Cd93*^{-/-} mice exhibit reduced vascular fibronectin deposition [208]. Despite its pro-angiogenic role, CD93, such as Multimerin-2 [197], also maintains endothelial barrier integrity, limiting cancer cell dissemination [210]. Thus, from the therapeutic point of view, targeting Multimerin-2-CD93 with antibodies or nanoparticles may offer novel anti-angiogenic strategies [211,212].

Another mechanism by which Multimerin-2 may affect vascular stability is the interaction with CD248, a receptor expressed by pericytes and stromal cells [204,213]. Multimerin-2 enhances pericyte adhesion, and *Multimerin-2*^{-/-} mice display poor pericyte coverage under both physiological and pathological conditions [197,214], although a direct role for CD248 in this process remains unconfirmed. Collectively, Multimerin-2 may act as a molecular bridge between ECs, via CD93/CLEC14A, and pericytes, possibly via CD248, reinforcing vessel stability. However, the complexity of these interactions warrants further investigation.

Emerging evidence also suggests possible crosstalk between Multimerin-2 and immune-related pathways. The 5'-UTR of Multimerin-2 mRNA is targeted by miR-1910-5p via CXCR4 [215], an important chemokine receptor regulating immune cell crosstalk [216]. This finding highlights a potential link between angiogenesis and immune signaling, opening new avenues for research in immune-TME interactions.

Despite the published evidences are scant, EMID1 and EMID2 also seem to shape cancer progression via microenvironmental and immune modulation. EMID1

disrupts cell adhesion, potentially altering stromal interactions and immune infiltration. For instance, in lung adenocarcinoma, high EMID1 correlates with increased B-cell infiltration [173]. EMID2 impacts on the TME by inhibiting TGF- β maturation, thus blocking CAF activation and ECM stiffening to reduce invasiveness and normalize the tumor mechanical niche [175]. Further studies are required to better define the role of these elusive molecules in shaping the TME.

Conclusions

Collectively, emerging evidence demonstrate that multiple EMILIN/Multimerin family members play significant roles in tumor biology through both direct and indirect mechanisms (Fig. 3). These glycoproteins show consistently dysregulated expression patterns across various malignancies. However, many of these analyses are based on mRNA levels (Table 1), which do not necessarily correlate with protein levels. Therefore, investigation into the proteolytic processes within the TME that substantially influence protein levels is required to fully understand their role. The structural homology shared among family members raises the intriguing possibility of functional compensation between paralogs, which could explain the complex phenotypes observed in single-gene perturbation studies.

To substantiate this hypothesis, systematic investigation using conditional knockout mouse models with combinatorial genetic ablation of different family members sharing similar expression patterns would be particularly informative. Such approaches could elucidate compensatory mechanisms while evaluating their collective impact on tumor initiation, growth, and metastatic progression.

While these findings underscore the therapeutic potential of targeting EMILIN/Multimerin proteins, critical knowledge gaps remain. The roles of EMILIN-3, EMID1, and EMID2 are poorly understood, with the exception of a recent EMID2 study that may catalyze future research. The molecular mechanisms through which EMILIN-3 and EMID1 modulate the TME are largely unknown, necessitating further investigation. Furthermore, a comprehensive characterization of the expression patterns of this family of molecules across tumor subtypes and stages is needed. Furthermore, the mechanistic basis of their tumor-modulatory functions requires elucidation, since their multidomain architecture suggests complex interaction with various receptors, cytokines, and signaling

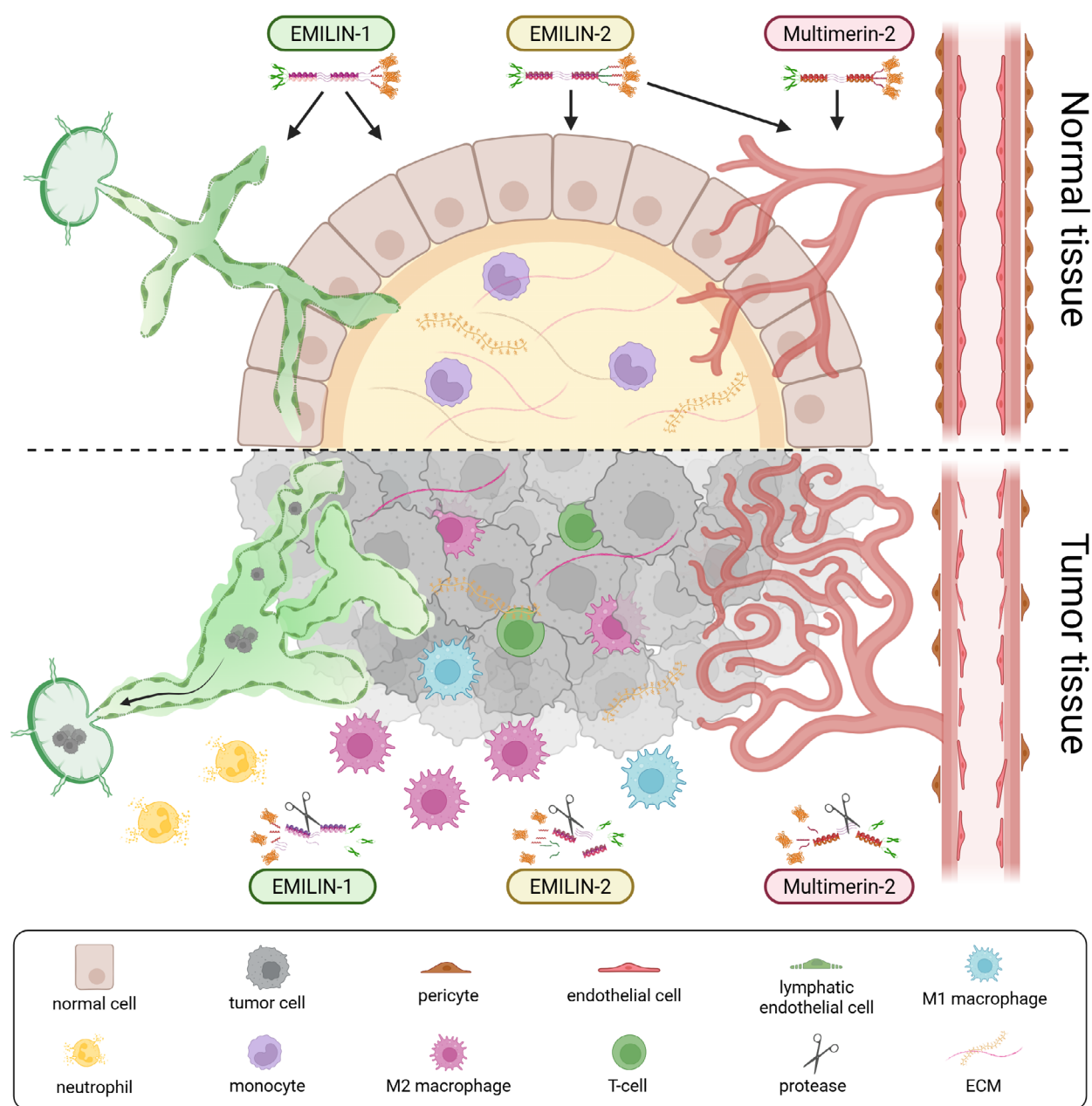


Fig. 3. EMILIN/Multimerin proteins regulate the TME homeostasis. In healthy tissues, EMILIN/Multimerin glycoproteins maintain vascular and lymphatic stability while suppressing proliferation through integrin binding (EMILIN-1/ $\alpha 4 \beta 1 / \alpha 9 \beta 1$) and Wnt pathway/apoptosis modulation (EMILIN-2). Tumor-associated proteases (e.g., MMPs, neutrophil elastase) degrade EMILIN-1, EMILIN-2 and Multimerin-2, with multifaceted consequences in the tumor microenvironment (TME). Degradation of EMILIN-1 and EMILIN-2 abolishes their antiproliferative signaling, enabling uncontrolled tumor growth. EMILIN-1 deficiency further destabilized lymphatic vessels, fostering metastatic dissemination and impairing lymphatic drainage, which sustains chronic inflammation. Conversely, loss of EMILIN-2 and Multimerin-2 disrupts vascular integrity, exacerbating hypoxia and compromising drug delivery. Additionally, EMILIN-2 depletion polarizes macrophages toward a pro-tumor M2 phenotype, reshaping immunosuppressive networks in the TME. Created with [BioRender.com](https://www.biorender.com).

pathways. Finally, although their potential as diagnostic and prognostic biomarkers is promising, further validation is essential. Future investigations should

focus on quantifying these fragments in biological fluids and rigorously assessing their correlation with clinical outcomes.

Table 1. Dysregulation of the EMILIN/Multimerin protein family in tumors. CDDP, cisplatin; DFS, disease-free survival; IF, Immunofluorescence; IHC, Immunohistochemistry; Mass Spec, Mass Spectrometry; N/A, not applicable; OS, overall survival; WB, Western Blot.

Molecule	Cancer type	Method of analyses	Fragment release	Clinical implication	References
EMILIN-1	Breast cancer	Mass Spec	Serum	Descriptive study	[100]
	Breast cancer	RNA sequencing + spatial transcriptomic	N/A	Correlaion with improved prognosis	[179]
	Breast cancer	cDNA microarray + <i>In silico</i> analyses	N/A	correlation with improved therapy response	[104,180]
	Ewing's sarcoma	<i>In silico</i> analyses	N/A	Descriptive study	[106]
	Osteosarcoma	Mass Spec	N/A	Descriptive study	[105]
	Ovarian cancer	mRN/A SAGE aN/Alyses	N/A	Descriptive study	[107]
	Gastric cancer	<i>In silico</i> analyses	N/A	Correlation with poor OS	[109]
	Low-Grade Glioma	<i>In silico</i> analyses	N/A	Correlation with poor OS/DFS	[111]
	Oropharyngeal cancer	<i>In silico</i> analyses	N/A	Correlation with improved OS	[113]
	Rhabdomyosarcoma	DNA methylation profile	N/A	Descriptive study	[101]
	Uterin carcinosarcoma	DNA methylation profile	N/A	Descriptive study	[102]
	Non-Small-Cell Lung cancer	<i>In silico</i> analyses + IHC	N/A	Descriptive study	[103]
	Breast cancer	<i>In silico</i> analyses	N/A	Correlation with improved OS	[77]
	Gastric cancer	<i>In silico</i> analyses + IF	N/A	Descriptive study	[45,108]
	Head and Neck Squamous Cell carcinoma	Mass Spec + Nanostring	N/A	Descriptive study	[112]
EMILIN-2	Ovarian cancer	Mass Spec + IHC	N/A	Correlation with improved OS	[119]
	Ovarian cancer	Mass Spec	Serum	Descriptive study	[125]
	Esophageal adenocarcinoma	Mass Spec	Serum	Descriptive study	[127]
	Breast cancer	DNA/RNA sequencing	N/A	Descriptive study	[186]
	Dermatofibrosarcoma	DNA/RNA sequencing	N/A	Descriptive study	[128–130]
	Renal cancer	<i>In silico</i> analyses	N/A	Correlation with poor OS	[131]
	Esophageal adenocarcinoma	Gene expression array	N/A	Descriptive study	[132]
	Low-Grade Glioma	<i>In silico</i> analyses	N/A	Correlation with poor OS	[111,133]
	Hepatocellular carcinoma	Bisulfite sequencing	N/A	Descriptive study	[121]
	Ovarian cancer	mRNA expression + IHC	N/A	Correlation with poor OS	[120]
	Colorectal cancer	Bisulfite sequencing	N/A	Descriptive study	[124]
	Breast cancer	CpG island microarray	N/A	Correlation with poor OS	[122]
	Breast cancer	<i>In silico</i> analyses	N/A	Correlation with poor OS	[117]
	Lung cancer	CpG island microarray	N/A	Correlation with poor OS	[123]
	Melanoma	<i>In silico</i> analyses	N/A	Correlation with poor OS and immunotherapy efficacy	[126]
EMILIN-3	Gastric cancer	IF	N/A	Descriptive study	[44]
	Low-Grade Glioma	<i>In silico</i> analyses	N/A	Correlation with poor OS	[111,134,135]
	Colorectal cancer	DNA sequencing	N/A	Descriptive study	[137]
	Metastatic colorectal cancer	Nanostring analyses	N/A	Descriptive study	[138]
Multimerin-1	Low-Grade Glioma	<i>In silico</i> analyses	N/A	Correlation with improved OS	[136]
	Pediatric Acute myeloid Leukemia	mRNA expression	N/A	Correlation with poor OS and relapses	[147]
	Pancreatic cancer	Mass Spec	Plasma	Descriptive study	[148]
	Cervical cancer	Mass Spec	Urine	Descriptive study	[149]
	Non Small Cell Lung cancer	Mass Spec	Plasma	Correlation with CDDP resistance	[151]
	Ovarian cancer	WBs/ELISA	Saliva	Descriptive study	[152,153]
	Multiple myeloma	Mass Spec	Serum	Descriptive study	[154]
	Oropharyngeal squamous cell carcinoma	mRN/A microarray	N/A	Descriptive study	[145]
	Hepatocellular carcinoma	Mass Spec	Serum	Descriptive study	[146]

Table 1. (Continued).

Molecule	Cancer type	Method of analyses	Fragment release	Clinical implication	References
Multimerin-2	Renal cancer	<i>In silico</i> analyses	N/A	Correlation with improved OS	[161]
	Ovarian cancer	Mass Spec	Plasma	Descriptive study	[166]
	Lung adenocarcinoma	Mass Spec	Pleura effusion	Descriptive study	[167]
	Breast cancer	Mass Spec	Urine	Descriptive study	[168]
	Thyroid cancer	Mass Spec	Tumor tissue	Descriptive study	[169]
	Low-Grade Glioma	<i>In silico</i> analyses	N/A	Correlation with poor OS	[111]
	Lung adenocarcinoma	AI application on TCGA	N/A	Correlation with poor OS	[162]
EMID1	Gastric Cancer	IF	N/A	Descriptive study	[164,165]
	Breast cancer	<i>In silico</i> analyses	N/A	Correlation with improved OS	[172]
	Prostate cancer	mRNA array + IHC	N/A	Descriptive study	[174]
EMID2	Lung adenocarcinoma	<i>In silico</i> analyses	N/A	Correlation with poor OS	[173]
	Pancreatic cancer	<i>In silico</i> analyses	N/A	Correlation with improved OS	[175]
	Lung adenocarcinoma	<i>In silico</i> analyses	N/A	Correlation with improved OS	[175]

Taken together, the pleiotropic nature of EMILIN/Multimerin family members positions them as promising, yet complex, therapeutic targets in oncology, demanding rigorous preclinical validation before considering clinical translation in oncology.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

EP, NC, EDS, GC, LC, and GS wrote parts of the manuscript; EDS created the images; SM, ET revised the manuscript; PS and MM conceived the subject, wrote part of the manuscript, and revised it.

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