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*Review Article*

# Progress of EGFL6 in angiogenesis and tumor development

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**Abstract:** The epidermal growth factor (EGF) superfamily includes the protein 6 with an epidermal growth factor-like protein (EGFL6). EGFL6 has a signal peptide domain with an amino terminus and a MAM domain with a carboxy terminus. There are four whole EGF-like repeat regions and one partial EGF-like repeat region. Three of these regions include calcium-binding structures and an arg-gly-asp (RGD) integrin interaction motif. The epidermal growth factor-like (EGFL) and EGF domains have identical amino acid residues. Cell division, differentiation, mortality, cell adhesion, and migration are all affected by EGFL6. EGFL proteins are involved in a broad range of biological activities, making it important in tumor development and angiogenesis. We highlighted the latest development of EGFL6 research on tumor proliferation, invasion, and migration in this review.

**Keywords:** EGFL6, angiogenesis, tumor

## Background and introduction

The epidermal growth factor-like protein (EGFL6) is a gene that codes for a protein. EGFL genes are involved in cell proliferation, differentiation, and apoptosis [1, 2]. Recently, the EGFL family, particularly EGFL6, has received much interest from researchers. The structure of EGFL6 is unusual, with three EGF-like repeat regions [3]. It has recently been discovered to be engaged in the proliferation and differentiation of tumor cells [4]. In our previous study [5] of limbal niche cells (LNC) and bone marrow derived mesenchymal stem cells (BMMSC), it was shown that the expression of EGFL6 gene in LNC was 273 times higher than that in BMMSC [5]. LNC cells are a type of support cell of limbal stem cell (LSC) [6]. EGFL6 plays an irreplaceable role in stem cells or in supporting stem cell proliferation and differentiation.

EGFL6 is involved in cell cycle regulation and is closely related to cell proliferation and development [7]. It is located on chromosome Xp22 [4]. EGFL6 has an impact on cell proliferation, differentiation, death, cell adhesion, and migration [8]. The EGFL family includes EGFL2, EGFL3, EGFL5, EGFL6, EGFL7, EGFL8, and EGFL9. The proteins produced by the EGFL gene are linked in a wide range of biological processes. EGFL plays a major role in tumor formation and angiogenesis [9]. EGFL7 is a one-of-a-kind member of the EGFL family. It can prevent the migration of vascular smooth muscle cells in blood arteries. Vascular endothelial cells modulate vascular endothelial cell adhesion and migration by secreting cytokines like EGFL7. EGFL7 plays a crucial role in vascular regeneration [10]. Many research on EGFL7 have been published in recent years, with the protein being found to be expressed in glioblastoma [11], liver cancer [12], breast cancer [13], lung cancer [14], and pancreatic cancer [15].

## EGFL6 gene and protein structure

Yeung et al. [16] identified and termed the epidermal growth factor-like protein 6 (EGFL6) in 1999. MAEG, MAM and EGF Domains-Containing Gene Protein, Epidermal Growth Factor-Like Protein 6, MAM and EGF Domain Containing, EGF-Like Protein 6, EGF Repeat-Containing Protein 6, EGF-Like-Domain, Multiple 6, and W80 are some known names of EGFL6 [17]. EGFL6 has been implicated in angiogenesis in a number of tumor tissues [18], the con-

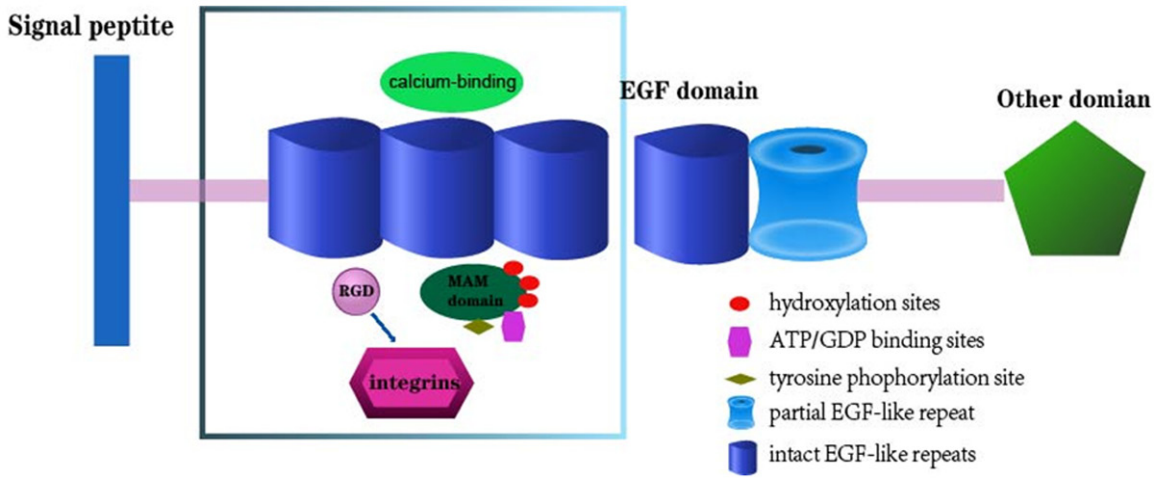


**Figure 1.** The structure of EGFL6.

trol of cell cycle [2], proliferation [19], and development [20], several research have shown. There are 30-40 amino acid residues similar in EGFL and EGF domains [21].

EGFL6 has an amino-terminated signal peptide domain and a carboxy-terminated MAM domain. There are four full EGF-like repeat regions and one incomplete EGF-like repeat region. Three of these regions feature calcium-binding structures and an arg-gly-asp (RGD) integrin interaction motif (**Figure 1**). It is assumed that these structures play a part in the cell adhesion process.

There are 12 exons and 19 introns and two transcriptional variations of mRNA in the EGFL6. Isoform 2 is encoded by variant 2 with one more amino acid compared with isoform 1. The CDS (coding sequence) section of isoform 1 is 1662 bp long, encoding 553 amino acids, and the CDS region of isoform 2 is 1665 bp long, encoding 554 amino acids. Chim et al. [22] found that EGFL6 is a secreted protein that occurs as a homologous complex.

The human EGFL6 protein has a total length of 553 amino acids and a molecular mass of 61 kDa. EGFL6 participates in a variety of physiological processes, including cell adhesion modulation, vascular endothelial cell proliferation, vascular endothelial cell migration, and angiogenesis [22-25]. EGFL6 is not expressed or low expressed in normal tissues or cells [26]. Blocking its expression has been demonstrated in studies to have no effect on wound healing. A vast number of studies have linked EGFL6 to the occurrence and progression of malignancies [21]. EGFL6 is expressed in several tumor tissues and is a key player in the genesis and progression of cancer. It is a target for cancer detection and therapy [16, 25, 27]. Proteins with an EGFL domain can activate the extracellular signal-regulated kinase (ERK), nuclear factor kappa B (NFB), mitogen-activated protein kinase (MAPK), protein kinase B (PKB), and Notch signal transduction pathways [21]. Chimpanzees, rhesus monkeys, dogs, cattle, mice, rats, chickens, zebrafish, and frogs all share the same EGFL6 gene. The protein expressed by EGFL6 is strongly positive in some malignancies [28]. EGFL6 is a candidate target for some tumor therapies [1, 28, 29].

## Research progress of EGFL6 in angiogenesis

Angiogenesis and endothelial cell function are both aided by EGF-like proteins. Research shows, EGFL7 is a secretory factor produced by vascular endothelial cells that controls the adhesion and migration of vascular endothelial cells while preventing the migration of vascular smooth muscle cells [30]. Similar structural and functional traits are shared by EGFL6 and EGFL7. Wang et al. [31] confirmed that the RGD domain in EGFL6 can promote angiogenesis in zebrafish. One of the receptors that recognizes the RGD motif is integrin 1. EGFL6 has been demonstrated to activate the AKT/ERK and Wnt/β-catenin signaling pathways. It is engaged in tumor angiogenesis through the ERK/AKT signaling pathway, suggesting that EGFL6 is

involved in tumor genesis, growth, and metastasis [21]. EGFL6 regulates embryonic angiogenesis and activates Akt/ERK signaling through integrin β1. EGFL6 upregulation can promote angiogenesis, suggesting that EGFL6 is involved in vascular development [4]. Chim et al. [22] used wound healing, tube formation assays, Chick Embryo Chorioallantoic Membrane Assay (CAM), and transwell migration tests in vitro and in vivo to show that EGFL6 stimulates endothelial cell migration and angiogenesis. Studies have demonstrated that EGFL6 is involved in every stage of angiogenesis. This includes promoting endothelial cell migration through scratch wound healing tests and transwell migration tests, strengthening tubular structures through test tube formation tests, and forming new blood vessels by CAM tests [21, 32]. To control angiogenesis in the neighborhood bone environment, some researchers believe that EGFL6 mediates a paracrine pathway between osteoblasts and vascular endothelial cells. By stimulating the extracellular matrix, osteoblasts enhance endothelial migration regulated protein kinase (ERK) [33, 34]. Studies have demonstrated that the 6-induced endothelial cell migration is mediated by the RGD peptide found in the EGFL6 protein. EGFL6 works with integrin to influence angiogenic activity [34].

### EGFL6 with obesity

Adipose-derived stromal vascular fraction (SVF) cells contain stem cell properties, particularly in obese patients. EGFL6 has been found to increase the proliferation of stromal vascular cells generated from adipose tissue. SVFs are a kind of heterogeneous cell that can support blood vessels and tissue generation. It has the ability for immune regulation and regeneration [21]. Oberauer et al. [24] found a significant upregulation of EGFL6 in obese humans. There is an increase in stromal vascular cells derived from adipose tissue. It has been demonstrated in studies that EGFL6's EGF-like repeats mediate selective adherence to SVF cell surfaces in an RGD dependent way, indicating that EGFL6 was involved in angiogenesis and tissue rebuilding.

### EGFL6 and tumor

The link between the expression of EGFL6, EGFL7, and EGFL8 and the kind of immune invasion in the tumor microenvironment was discovered by Shi et al. [9] using TCGA data. In several major cancers studies, EGFL6 was found to be strongly expressed. Blocking EGFL6 was often utilized to decrease tumor angiogenesis and played an anti-tumor effect. Studies have shown that EGFL6 played a distinct role in tumor angiogenesis [26, 29]. The difference in the EGFL6 expression between endothelium damaged cells and tumor cells was examined by Noh and coworkers [26], in mice by occluding the femoral artery in the rear limb [35]. They discovered that in ischemic tissue, EGFL6 levels in tumor endothelial cells were considerably greater than in non-ischemic tissue. When oxygen levels were normal, EGFL6 activity was much lower than when hypoxia was present. TWIST1 boosts EGFL6 to encourage angiogenesis brought on by hypoxia. EGFL6 has an RGD motif in its structure, which can interact with integrins. Noh et al. [26] found that EGFL6 promotes tumor-associated tube formation and endothelial cell migration by regulating Tie2/AKT signaling through the 51 integrin. Angiogenesis can be controlled by the integrin/Tie2/AKT signaling pathway. Through Tie2/PI3K/AKT signaling, EGFL6 plays a role in tumor angiogenesis. Cell adhesion, angiogenesis, migration, invasion, and adherent independent growth are all mechanisms that contribute to tumor invasion and metastasis [36-39].

Cancer cells' entrance into blood arteries and lymphatics is aided by the extracellular matrix's degrading (ECM). The cysteines and glycine domains of the epidermal EGF superfamily are conserved in 30-40 residues. These domains have many EGF repeats [11]. Secreted cell surface chemicals are normally responsible for cell development, and cycle and proliferation regulation. EGFL6 is a member of the epidermal growth factor superfamily that resembles other superfamily members physically and possesses unique structural characteristics. EGFL6 is overexpressed in numerous tumor tissues, but not expressed or under expressed in normal tissues, as stated in research articles [21, 32]. EGFL6's presence in cancers shows that EGFL6 had a role in the onset and progression of cancer [4, 40, 41].

### EGFL6 and breast cancer

EGFL6 is abundant in blood vessels of tumor, but it has no effect on normal wound healing

[21]. As a result, researchers identified EGFL6 as a target for preventing tumor blood vessels from forming. Larimer et al. [41] discovered ligands linked with EGFL6 in breast cancer tumor tissue, suggesting that EGFL6 was engaged in angiogenesis in breast cancer. Through in vitro and in vivo investigations, An et al. [4] established that breast cancer cells' invasion and metastasis were speed up by EGFL6, promoting tumor angiogenesis. Findings show that EGFL6 appears to sustain the expression of breast cancer-associated stem cells and initiate epithelial mesenchymal transition (EMT) in breast cancer. EGFL6 has been found to be positively associated the aggressiveness of breast cancer. EGFL6 plays a crucial part in the onset and progression of breast cancer [4].

### Study on EGFL6 in ovarian cancer

Bai et al. [40] found the tumor stem cells (TSC) in ovarian cancer were stimulated to migrate and divide in an asymmetric manner. This assisted EGFL6 to increase the growth and metastasis of ovarian cancer. EGFL6 was shown, in various researches, to be expressed in both vascular and tumor cells. They discovered that EGFL6 was expressed equally in vascular endothelium and tumor cells, and that EGFL6 enhanced the development of transplanted tumors utilizing a tumor vascular model. EGFL6 expression in vascular endothelium is associated with increased metastasis of cancer cells. Inhibiting EGFL6 expression stops ovarian cancer cells from moving into the ovarian circulation. This evidence showed that EGFL6 was important for the ovarian microenvironment [29]. After ovarian cancer cell proliferation and metastasis, EGFL6 expression is suppressed. EGFL6 can promote the development of ovarian tumor. Human and mouse ovaries have high levels of EGFL6, which has an impact on fertility [42].

### EGFL6 in colorectal cancer

In the genesis and progression of colorectal cancer, EGFL6 plays a critical role [19]. Colorectal cancer tissues have high levels of EGFL6. Normal colorectal tissues have low levels [43]. EGFL6 controls the cell cycle and suppresses apoptosis, as proven in vitro and in vivo research [9, 19, 29, 44]. The involvement of EGFL6 in tumor genesis and development through the ERK signaling pathway is the focus of most current investigations on EGFL6 in malignancies. Zhang et al. [19] initially related EGFL6's activity to the Wnt/-catenin pathway, after exploring the role of EGFL6 in colorectal cancer, they discovered that removing EGFL6 lowered the levels of its downstream target TCF7L2 and β-catenin. These findings show that through stimulating the Wnt/-catenin pathway, EGFL 6 plays a major role in tumorigenesis [7]. In benign meningiomas, nasopharyngeal carcinomas, lung cancers, and oral squamous cell carcinomas, EGFL6 was overexpressed [45-47]. In patients with oral squamous cell carcinoma, Chuang et al. [45] investigated the association between plasma EGFL6 levels and clinicopathological characteristics. Their findings demonstrated that EGFL6 was crucial for the initiation and development of oral squamous cell carcinoma. In patients with non-oral squamous cell carcinoma, the presence of the protein EGFL6 can be utilized as a tumor marker to assess the likelihood of developing oral squamous cell carcinoma. EGFL6 activates the AKT pathway to encourage the migration of nasopharyngeal cancer cells [46]. Research demonstrated that high EGFL6 expression has been linked to a poor prognosis for lung adenocarcinoma, particularly in young patients [47]. Wang et al. [25] proposed that integrin-mediated and PI3K/Akt activation signaling are involved in the pathogenesis of anaplastic and benign meningiomas. They state that serum and tissues from benign meningiomas overexpress EGFL6. Studies on EGFL6 in different malignancies demonstrate that EGFL6 is crucial to the origin and growth of tumors [1, 28, 29].

Angiogenesis is required for tumor development and spread, because cancer cells rely on blood arteries for oxygen and nutrients. EGFL6 can be employed as a target to block tumor angiogenesis. EGFL6 can be used to treat cancers by blocking tumor angiogenesis [48]. Endothelial cells were extracted from 10 instances of high-grade serous ovarian cancer (HGSC), 5 cases of normal ovarian tissue, and 7 cases of healed wound patients by Noh and his colleagues [26]. Genomic analysis was performed after RNA extraction. It was shown that EGFL6 was mostly expressed in tumor endothelial cells, but not in healthy ovarian or wound endothelial cells. Ovarian tumor angiogenesis is hypothesized to be aided by EGFL6, which is

highly expressed in ovarian cancer tissues and is thought to contribute to the disease's development [40, 41]. In their wound healing mouse model, EGFL6 expression was muted. Effect analysis showed that EGFL6 reduced KOV3ip1 load, tumor microvascular density, and tumor tissue proliferation index. Blocking EGFL6 expression in wound tissue had little effect on normal wound healing, in contrast to antagonizing tumor angiogenesis [26].

## EGFL6 in stem cells

Jiang et al. [20] found that nude mouse hair follicles seldom retained lanceolate complexes, and EGFL6 was absent in aberrant hair follicles. In contrast, following innervation of hair follicles, EGFL6 was expressed in the central isthmus area of nude mouse hair follicles regenerated by stem cell chamber transplantation. Long-term dermal denervation, but not short-term dermal denervation, causes TSC degeneration and EGFL6 expression loss. Adipose-derived mesenchymal stem cells (ADSCs) are pluripotent stem cells that have been extracted from adipose tissue [49]. Osteoblasts are separated after induction and take a crucial part in bone healing. New research found the ability of ADSCs isolated from adipose tissue to differentiate into osteoblasts was shown to be dramatically decreased following EGFL6 knockdown [49]. Including recombinant EGFL6 protein, this capacity was restored. The impact of EGFL6 recombinant protein on osteogenic differentiation was decreased when BMP2 was knocked off. Through the BMP2/SMAD4 signaling pathway, EGFL6 recombinant protein stimulates osteogenic development of ADSCs. This is a promising target for ADSC osteogenic differentiation. We also found that EGFL6 was highly expressed in LNC [5].

## Future clinical applications of EGFL6

Blocking EGFL6 expression in wound tissue had little effect on normal wound healing, in contrast to antagonizing tumor angiogenesis [40]. Breast cancer tumor models are treated with an EGFL6-neutralizing antibody both in vivo and in vitro, which inhibits tumor development by reducing cancer cell proliferation and migration [4]. This resulted in a proposed theory that EGFL6 is a viable therapeutic target for tumor detection and therapy. For the creation of novel tumor diagnostic indicators, prognostic markers, or therapeutic targets, more researches into this mode of action in human cancers will be important.

EGFL6, a secretory protein, regulates endothelial cell behavior during normal and pathological angiogenesis by acting on endothelial cells. It is abundantly expressed in tumor-associated endothelial cells. Its function in angiogenesis is mediated in part by ERK/AKT signaling, which helps tumors grow. Human tumor cells that overexpress EGFL6 is associated with the growth, metastasis, and progression of tumors. It regulates several carcinogenic signaling pathways. Researches on the mechanism of the EGFL6 gene in tumor genesis and development can provide fresh concepts for scientific exploration of the tumor. EGFL6 maybe a new targets for tumor gene diagnosis and it maybe provide a new scientific foundation and theoretical underpinning for the identification of viable pharmacological targets. As a result, cancer patients' metastasis and death rates are reduced, and their survival rates are improved.

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## Disclosure of conflict of interest

None.

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