Review

ELTD1 Review: New Regulator of Angiogenesis in Glioma

IULIANA BUZATU[1], DANIELA ELISE TACHE[2],
ELENA VICTORIA MANEA CARNELUTI[2], OVIDIU ZLATIAN[3]

[1]*Clinical Hospital of Fundeni, Bucharest, Romania*

[2]*Department of Biochemistry, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*

[3]*Department of Microbiology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*

ABSTRACT: Glioblastoma (GBM) is a severe brain cancer in which angiogenesis is controlled by G protein-coupled receptors (GPCRs), such as Epidermal Growth Factor Latrophilin and seven transmembrane domain-containing protein 1 (ELTD1), which are crucial for tumor progression. ELTD1 is an understudied GPCR with a broad expression profile in various tissues, including the human brain, especially in the cerebral cortex. It plays a significant role in angiogenesis and tumorigenesis and is regulated by interconnected VEGF and DLL4/Notch pathways. ELTD1 also modulates the JAK/STAT3/HIF-1α signaling axis, affecting the response of cells to low-oxygen conditions and promoting cell proliferation. However, their specific ligands and functional mechanisms remain unclear. ELTD1 expression is associated with different outcomes in various cancers. For example, in GBM, higher ELTD1 levels are linked to more mature and less leaky blood vessels, potentially enhancing drug delivery and therapeutic success. It also has divergent prognostic implications in renal, ovarian, and colorectal cancer. Additionally, ELTD1 overexpression in central nervous system endothelial cells suggests that it is a potential biomarker for multiple sclerosis. Therapeutically, blocking ELTD1 inhibits vessel formation, possibly slowing tumor growth. Initial therapies used polyclonal antibodies, but the shift has been towards more targeted monoclonal antibodies, particularly in preclinical glioma models. This review aimed to translate these insights into effective clinical treatments. However, several gaps remain in our knowledge regarding ELTD1 ligands and their potential involvement in other physiological or pathological processes that future research can address to elucidate the role of ELTD1 in cancer, through angiogenesis and other intracellular pathways.

KEYWORDS: *ELTD1, angiogenesis, glioblastoma.*

Introduction

Glioblastoma (GBM) is a very aggressive type of cancer originating from glial cells, with approximately 3 cases in 100.000 people yearly, ranking 19th in terms of incidence worldwide [1].

The risk factors for GBM include genetic disorders (neurofibromatosis, Li-Fraumeni syndrome), previous radiation therapy, smoking, and obesity [2].

GBMs represent 15% of all brain tumors that can develop from normal brain cells or evolve from an existing low-grade astrocytoma [3].

GBMs manifest with unregulated vascular angiogenesis, high invasiveness, tumor vascularization, and resistance to apoptosis.

The median survival of treated patients is currently 10-13 months after diagnosis and the 5 years survival is <3%.

Most noticeably, survival without treatment is approximately 3 months [4].

In 2021, the World Health Organization (WHO) released a new classification system for adult GBMs based on the expression of Isocitrate Dehydrogenase (IDH), which defines three types (IDH-mutant astrocytoma, IDH-mutant oligodendroglioma 1p/19q-codeleted, and IDH-wildtype glioblastoma) [5].

A key mechanism in the development of the glioblastomas, as in many forms of cancer, is angiogenesis, which is defined as the formation of new blood vessels, as it provides nutrients and oxygen necessary for tumor growth.

This process is one of the main therapeutic pathways employed in modern cancer therapies [6,7].

The vast majority of steps in the angiogenic process are regulated by G protein-coupled receptors (GPCRs), which belong to the largest family of membrane receptors (~900 genes in the human genome) [8] and are expressed in endothelial cells (ECs), vascular smooth muscle cells, and endothelial progenitors.

They detect a wide array of extracellular stimuli, including hormones, proteins, phospholipids, peptides and ions [9].

From these receptors, we focused on the Epidermal Growth Factor Latrophilin and seven transmembrane domain-containing protein 1 (ELTD1), an adhesion GPCR in the Family 1, and latrophillin-like receptors.

The purpose of this review is to shed light on the role of ELTD1 in the development and

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progression of GBM, with a particular focus on its role in angiogenesis and tumorigenesis.

Despite the crucial role of angiogenesis in GBM development, ELTD1 has not yet been sufficiently studied.

This review summarizes existing research on ELTD1 biological processes, signaling pathways, and its potential as a therapeutic target in GBM.

In doing so, we intend to show the systematic contributions of ELTD1 to GBM angiogenesis and tumorigenesis, highlighting its significance in cancer, which has a notably poor prognosis and limited treatment options.

ELTD1 structure

ELTD1 gene is located on human chromosome 1 and contains 15 exons comprising a 3527-nucleotide chain that translates into a 690 amino acid protein [10].

ELTD1 structure [10] can be compartmented based on topographical properties or cleavage-based properties in 3 compartments:

a) extra-cellular domain (ECD) which contains an EGF domain, EGF Ca binding domain (adhesion domain) and 'GPCR autoproteolysis inducing domain' (GAIN) (that contains GPS: GPCR proteolysis site);

b) 7-transmembrane domain (7TM);

c) short intracellular domain (ICD) [10].

Based on the GPS cleavage site, ELTD1 can be divided into a) N-terminal Fragment (NTF) and b) C-terminal fragment (CTF) (Figure 1).

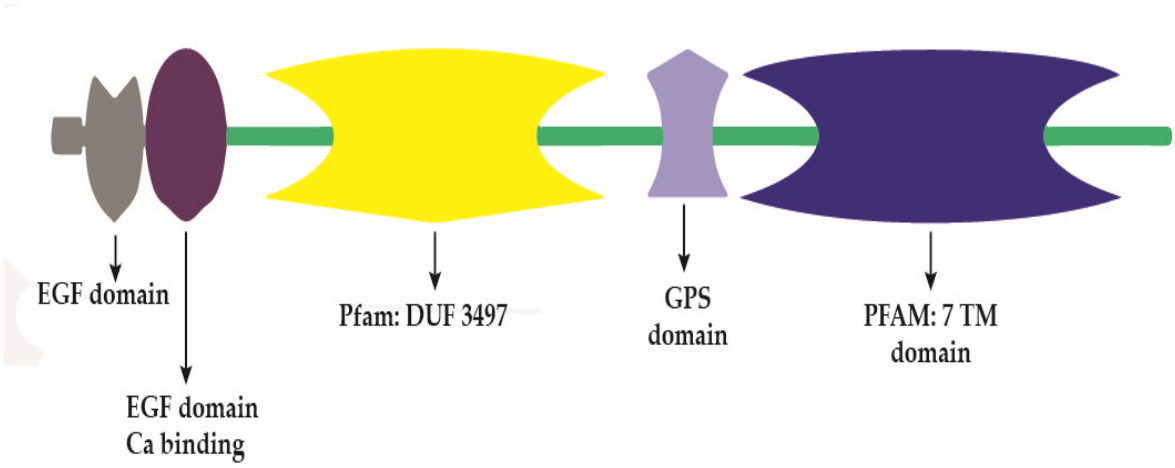

Figure 1. Molecular structure of ELTD1. EGF: Epithelial Growth Factor (adapted from [11]). GPS: GPCR proteolytic site. TM: transmembrane domain. Pfam: database of protein sequences. DUF: Domain of Unknown Function.

Expression in human tissues

ELTD1 expression on the cell surface was studied using fluorescence-activated cell sorting analysis of T455A cells[12].

ELTD1 is highly expressed in the adipose tissue, spleen, urinary and gall bladder, thyroid gland, placenta, endometrium, heart, and lungs.

At low levels, it is expressed in many tissues, as angiogenesis is a generalized process in the human body [13].

In the human brain, ELTD1 is expressed in many areas but is predominant in the cerebral cortex [12] (Figure 2).

New studies have reported that ELTD1 can be a potential biomarker for multiple sclerosis, as it is overexpressed in endothelial cells from the central nervous system in these patients and can be a marker of vascular changes [14].

Role in cell signaling and angiogenesis

Some of the functions of ELTD1 have been elucidated (Figure 3), but it is probable that this receptor plays other unknown roles.

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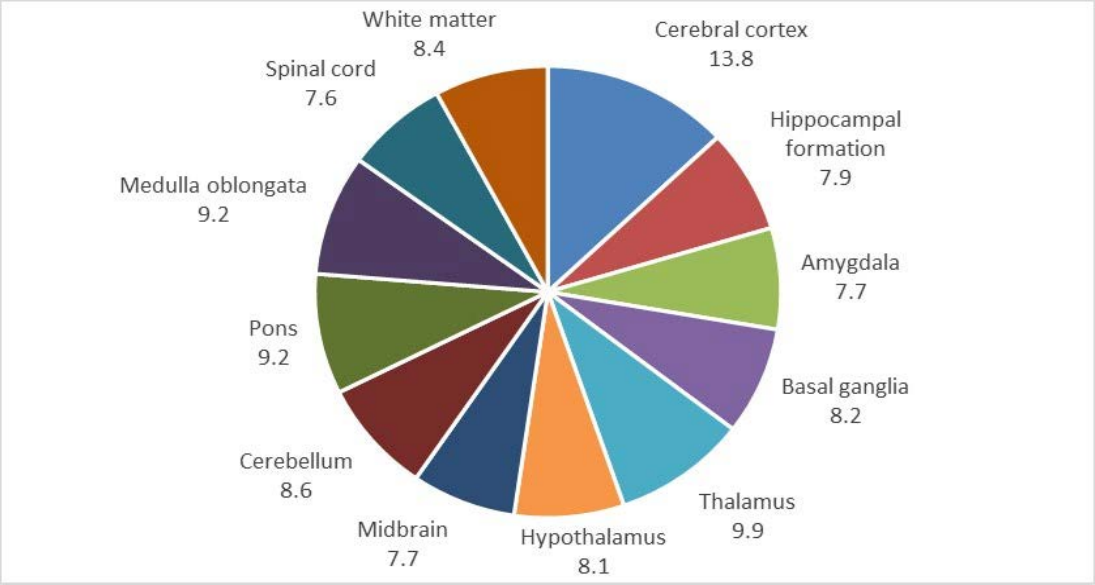

Figure 2. Expression pattern in the human brain of ELTD1. Expression level is in normalized transcription level values (nTPM). Data from the Human Protein Atlas [12].

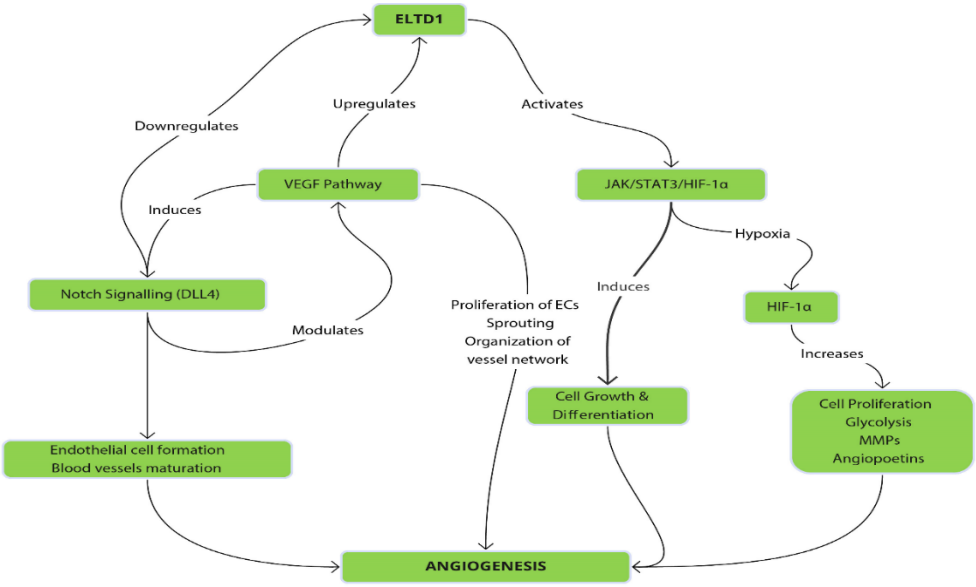

Figure 3. Molecular mechanisms of ELTD1 involvement in angiogenesis.

The most well-known function is the regulation of angiogenesis, which leads to tumor growth and metastasis by its involvement in the adhesion of ECs [15].

ELTD1 blockade does not affect the viability of cultured ECs, suggesting that it is not essential for their survival [15].

It was shown that ELTD1 expression in the normal vasculature is regulated by two distinct pathways.

These pathways regulate embryonic vascular development and angiogenesis in tumors.

The Vascular Endothelial Growth Factor (VEGF) pathway increases ELTD1 expression through VEGFR2, a ligand of VEGF; in turn, ELTD1 increases VEGFR2 levels.

The DLL4/Notch signaling pathway decreases ELTD1 expression (via delta-like ligand 4 (DLL4) [15-17].

The VEGF pathway has several meeting points with DLL4/Notch signaling.

The VEGF pathway induces DLL4/Notch signaling, while DLL4/Notch signaling modulates the VEGF pathway.

VEGF plays a crucial role in angiogenesis and formation of new blood vessels.

It promotes proliferation of ECs, inhibits their apoptosis, induces sprouting of blood vessels,

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growth of large vessels, and organization of the vessel network [7].

This is important because it induces vascular permeability to plasma coagulation factors, leading to a prethrombotic state that favors intravascular thrombosis.

VEGF also plays a role in the response of tumor cells to hypoxia or oxygen deprivation.

Hypoxic cells upregulate the expression of VEGF, triggering hyperplasia of endothelial cells and contributing to vascular hyperplasia [18].

Therefore, it is a key factor in tumor growth and progression.

Notch signaling is involved in cell proliferation, differentiation, and angiogenesis [19].

DLL4/Notch signaling was demonstrated to suppress endothelial cell formation.

Indeed, the blockade of this pathway on one side increases non-productive angiogenesis, but on the other side, reduces the growth of tumors, independent of tumor sensitivity to anti-VEGF therapies.

Immunohistochemistry and RNA sequencing data suggest that ELTD1 disrupts the Notch1 signaling pathway[20].

The Notch pathway is known to influence the expression of several genes.

These include hairy enhancer of split (HES) and HES-related proteins (HEY), both of which are crucial for lineage-commitment choices.

Cell cycle regulators such as p21/Waf1, Cyclin D1 (CD1), CD3, and c-Myc, a regulator of stem cell biology, are also influenced.

Other genes include the EGFR-related gene HER2, nuclear factor kappa B (NF-κB), insulin-like growth factor 1-receptor (IGF1-R), survivin, snail homolog 2 (SLUG), SOX2, and paired box (PAX) 5 [21].

All these genes are directly associated with tumorigenesis.

Recently it was shown that ELTD1 activates JAK/STAT3/HIF-1α signaling axis [22].

Knockdown of ELTD1 with short hairpin RNAs in glioma cell lines U-87MG and U-138MG led to a decrease in the protein levels of p-JAK, p-STAT3, Hypoxia-Inducible Factor 1α (HIF-1α), and Frataxin compared to control cells, while the other protein levels were unchanged [22].

The same study showed that ELTD1 upregulates the expression of HIF-1α [22].

STATs (signal transducers and activators of transcription) are cytoplasmic transcription factors that transmit signals initiated by cytokines and growth factors.

They are activated through phosphorylation of their tyrosine residues by Janus kinases (JAK) or kinases induced by growth factors, leading to their dimerization and nuclear translocation.

In the nucleus, STATs act as transcription factors with diverse downstream effects.

STAT1 is involved in cell growth arrest and apoptosis induction, and acts as a tumor suppressor molecule.

In contrast, STAT3 and 5 seem to promote cell cycle progression and malignant transformation and prevent apoptosis.

Abnormal activation of STATs, especially STAT3 and STAT5, has been observed in many human cancers, including gliomas.

In tumor cells, STAT3 inhibits the degradation of Hypoxia-Inducible Factor 1α (HIF-1α), increasing its levels, which leads to increased cell proliferation [23].

HIF-1α plays a critical role in the regulation of cellular responses to hypoxia.

Under normal conditions, when there is sufficient oxygen availability, HIF-1a is targeted for destruction by the Von Hippel-Lindau (VHL) tumor suppressor protein.

However, when cells are exposed to hypoxia, HIF-1α is not destroyed and instead forms a complex with p300 and CBP proteins, which activates specific genes by binding to the hypoxia-responsive element (HRE).

One of the most critical genes upregulated in this process is VEGF, which is essential for the formation of new blood vessels.

HIF-1α binds to a specific site in the VEGF promoter region to ensure proper expression of the gene and also helps in the proper folding of the VEGF protein, which is crucial because low-oxygen conditions can disrupt protein shape.

In addition to VEGF, HIF-1 activates a range of other genes, including glycolysis enzymes, matrix metalloproteinases (MMPs), transforming growth factors (TGFs), and angiopoietins, which are collectively critical for the process of neovascularization in glioma [23].

Despite its important role in angiogenesis, ELTD1 upregulation in tumor-associated ECs is not fully understood.

It is very probable that additional involvement of VEGF and basic fibroblast growth factor (bFGF) also contribute to angiogenesis in tumors [24].

Even though all the research efforts, little is known about the ligands of ELTD1, which implies that many molecular mechanisms involved are still unknown.

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Role in cancer

Various studies on ELTD1 expression in multiple cancer types have demonstrated an upregulation in EC proliferation associated with tumor blood vessels, but, on the other hand, higher expression was also associated with a favorable prognosis (Figure 4).

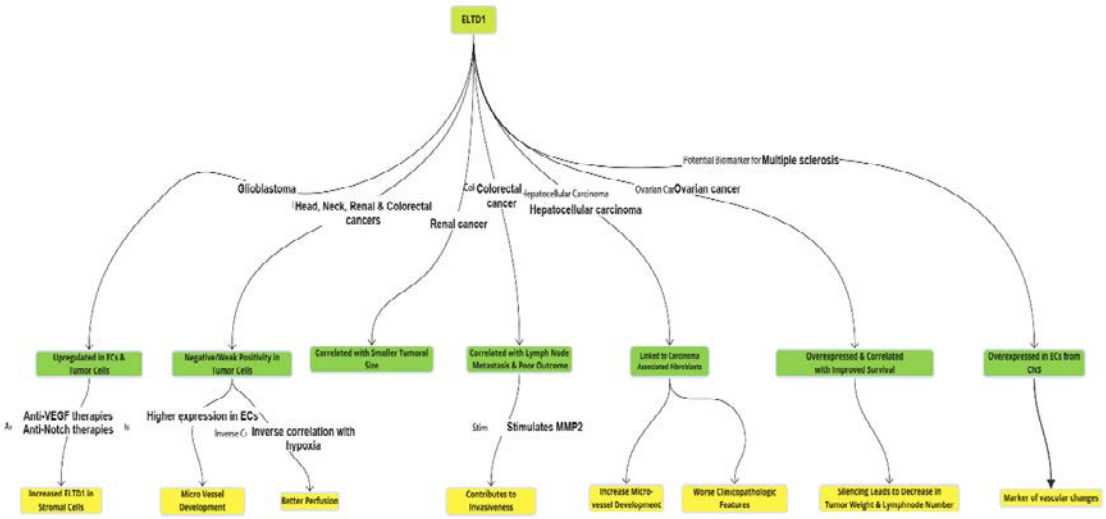

Figure 4. Involvement of ELTD1 in human cancers.

ELTD1 mRNA and ELTD1 protein levels are increased in tumor cells [15].

ELTD1 knockdown reduces cell proliferation and increases apoptosis of ECs [15].

Based on these results, it was proposed the "vessel maturity" hypothesis, that ELTD1 contributes to the maturation of the blood vessels.

Usually in tumors, the blood vessels are tortuous, immature, and very leaky, and the drug delivery rate to the tumor is low; therefore, more mature blood vessels, less leaky and less tortuous, can greatly improve the drug delivery rate and contribute to therapeutic success [24].

In GBM, ELTD1 is upregulated in ECs and tumor cells [25].

Anti-VEGF and anti-Notch treatments increased ELTD1 expression in stromal cells of glioblastoma [15].

A strong argument for the involvement of ELTD1 in gliomas is that even though this receptor is expressed in several human tissues, its expression in both normal and tumoral samples is observed only in gliomas [26].

In head and neck, colorectal, and renal cancers, ELTD1 showed predominantly negative or weak expression levels.

Compared to normal tissue, ELTD1 expression was clearly higher in tumor-associated ECs, and higher expression correlated with microvessel development [25].

Furthermore, ELTD1 messenger RNA (mRNA) was inversely correlated with hypoxia signature [27] or hypoxia-inducible gene CA9, suggesting that tumors with high ELTD1 expression are better perfused [15].

In renal cancer, increased ELTD1 expression was associated with smaller tumor size and improved survival [15].

In colorectal cancer, increased expression of ELTD1 correlates with lymph node metastasis and, consequently, with poor outcomes.

In vitro studies have shown that ELTD1 stimulates the transcriptional activity of MMP2, which contributes to the invasiveness of cancer cells [28,29].

In hepatocellular carcinoma, ELTD1 role was linked to carcinoma-associated fibroblasts, a sub-population of fibroblasts that can modulate carcinoma progression through the tumor microenvironment [30].

In addition, ELTD1 staining has been shown to increase microvessel development via CD34 staining [31,32].

ELTD1 expression in hepatocellular carcinoma is inversely correlated with worse clinicopathologic features [32].

ELTD1 was reported to be overexpressed in ovarian cancer and was positively correlated with improved survival in these patients.

In addition, silencing of ELTD1 in murine models led to a significant decrease in tumor weight and lymph node number [25].

Clinical implications

Several approaches have been used to inhibit tumor angiogenesis, including immunotherapy, nanomedicine, repurposing of older drugs, use of phytochemicals, and precision medicine [33].

One of the most promising anti-angiogenic therapies is anti-vascular endothelial growth factor (VEGF) therapy.

Although the theoretical basis is strong, studies have shown limited clinical benefits of anti-VEGF therapy, although several phase III trials have demonstrated the success of anti-VEGF agents in several major cancers.

Numerous tumors exhibit resistance to anti-VEGF therapy, which can be intrinsic or acquired during therapy [24].

Therefore, researchers have attempted to identify new targets that promote tumor angiogenesis.

As discussed above, DLL4/Notch blockade suppresses endothelial cell formation and reduces tumor growth.

Pre-clinical studies have shown that combined therapies that target both pathways synergistically reduce tumor growth [34].

It seems that ELTD1 blockage damages endothelial sprouting and vessel formation, both in vitro and in vivo, which in turn slows tumor growth and improves survival.

Some anti-ELTD1 therapies used polyclonal antibodies (pAbs), which showed efficacy in preclinical studies [35].

However, it is widely accepted that pAb binding is random, with many sites being blocked to various degrees.

Then were developed monoclonal anti-ELTD1 therapies that began to be optimized to select monoclonal antibodies (mABs).

Many preclinical studies have used G55 xenograft glioma models [20,36-38].

All these data regarding ELTD1 structure and function lead to studies that try to translate it into clinically effective treatments.

Most of the clinical studies used the tumor volume as an output measurement of treatment effect as assessed by magnetic resonance imaging (MRI) and animal survival.

Vascular perfusion images were used to assess the effects on tumor vascularization.

Some studies have used immunochemistry and molecular targeting imaging to evaluate binding specificity against various tumor regions [20,36-40].

Some studies have shown that the blood-brain barrier (BBB) can be disrupted in patients with GBM.

Therefore, some mAbs may not cross the BBB and infiltrate the tumor due to their high molecular volume.

To overcome these limitations, Smith et al. used a molecular-targeting approach for GBM [39].

Zalles et al. worked in a G55 xenograft mouse model to optimize anti-ELTD1 mAbs using an svFc antibody fragment, which led to increased survival and decreased tumor volumes [20].

Experimental studies have explored the effects of anti-ELTD1 therapy on the JAK/STAT3/HIF-1α signaling axis.

Knockdown of ELTD1 with short hairpin RNAs in glioma cell lines U-87MG and U-138MG led to a decrease in p-JAK, p-STAT3, HIF-1α, and Frataxin protein levels compared to control cells, whereas the other protein levels remained unchanged [22].

Conclusions

Recent studies have extensively investigated the expression of ELTD1 and its potential involvement in critical processes, such as tumor angiogenesis, migration, and invasion.

The well-established role of ELTD1 in cell adhesion further supports its role in these pathways.

Notably, gliomas exhibit both normal and tumor cell expression of ELTD1, emphasizing the possibility of identifying novel molecular targets for targeted anticancer therapies.

However, several gaps remain in our knowledge regarding ELTD1 ligands and their potential involvement in other physiological or pathological processes that future research can address.

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Iuliana Buzatu and Daniela Elise Tache share equal contributions to this work.

Conflict of interests

The authors declare no conflict of interest.

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Corresponding Author: Elena Victoria Manea (Carneluti), Department of Biochemistry, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, e-mail: elena.manea.v@gmail.com