Roles of Embryonic Lethal Abnormal Vision-Like RNA Binding Proteins in Cancer and Beyond

Haijian Cai†, Dandan Zheng†, Yizhu Yao, Lehe Yang*, Xiaoying Huang* and Liangxing Wang*

The First Affiliated Hospital, Wenzhou Medical University, Wenzhou, China

Embryonic lethal abnormal vision-like (ELAVL) proteins are RNA binding proteins that were originally discovered as indispensable regulators of the development and functioning of the nervous system. Subsequent studies have shown that ELAVL proteins not only exist in the nervous system, but also have regulatory effects in other tissues. ELAVL proteins have attracted attention as potential therapeutic targets because they stabilize multiple mRNAs by binding within the 3′-untranslated region and thus promote the development of tumors, including hepatocellular carcinoma, pancreatic cancer, ovarian cancer, breast cancer, colorectal carcinoma and lung cancer. Previous studies have focused on these important relationships with downstream mRNAs, but emerging studies suggest that ELAVL proteins also interact with non-coding RNAs. In this review, we will summarize the relationship of the ELAVL protein family with mRNA and non-coding RNA and the roles of ELAVL protein family members in a variety of physiological and pathological processes.

Keywords: ELAVL proteins, RNA binding proteins, non-coding RNAs, post-transcriptional regulation, cancers

INTRODUCTION

The embryonic lethal abnormal vision-like (ELAVL) proteins in fish, frogs, and mammals are defined as RNA-binding proteins (RBPs), and they play important roles in post-transcriptional regulation (Campos et al., 1985). ELAVL proteins were first discovered in Drosophila due to their ability to interact with AU-rich element (ARE)-containing transcripts (Campos et al., 1985). Each member of the ELAVL protein family, which includes ELAVL1-4 (HuR HuB, HuC, HuD) (Figure 1), consists of three similar and conserved RNA recognition motifs (RRM) (Toba and White, 2008; Colombrita et al., 2013). The sequence of a hinge region between RRMs 2 and 3 differs among the four family members (Good, 1995), and its presence is key to the ability of these proteins to shuttle into and out of the nucleus (Fan and Steitz, 1998a).

Biologically, ELAVL proteins were originally discovered as indispensable regulators of nervous system development and physiological function (Rogulja-Ortmann et al., 2014; Wang et al., 2019a; Zhao et al., 2020a). Interestingly, subsequent studies have shown that they not only exist in the nervous system, but also have regulatory effects in other tissues, including hepatocytes (Wang et al., 2021), fat cells (Siang et al., 2020), vascular smooth muscle cells (Liu et al., 2020a), and intestinal epithelial cells (Liu et al., 2019).

Previous studies have mainly focused on the relationship between ELAVL proteins and downstream mRNA transcripts, and less attention has been paid to interactions between ELAVLs and non-coding RNA (ncRNA) molecules. The regulation and metabolism of ncRNA is an emerging research topic, and ncRNAs have been shown to play important roles in a variety of fields, such as cancer (Deschenes-Furry et al., 2007; Schultz et al., 2020), inflammation (Wen et al.,...
MEMBERS OF THE ELAVL FAMILY

ELAVL1, also known as human antigen R (HuR), has been established as a tumor-specific antigen in colorectal carcinoma (Wang et al., 2000) and tumors of the central nervous system (Nabors et al., 2001). This protein is a widely expressed RBP whose function in many cell types has been elucidated. The gene encoding human ELAVL1 is localized to chromosome 19p13.2, and while the protein is mainly localized to the nucleus, it will translocate to the cytoplasm following stimulation by a variety of extracellular stimuli (Chand et al., 2017).

The consequences for an mRNA after ELAVL1 binding to its ARE depend on the mRNA itself and the cell type. When the target ARE, which usually contains multiple AUUUA repeats, appears in the 3′-untranslated regions (UTRs) of an mRNA, ELAVL1 binding often results in mRNA instability (Fan et al., 1997), and thus selective binding of ELAVL1 to the ARE at the 3′ end of an mRNA can lead to rapid degradation (Myer et al., 1997). However, in most cases, ELAVL1 plays an important role in stabilizing the mRNA sequence. Competitive binding to mRNA in the 3′-UTR by ELAVL1 prevents exonuclease- or endonuclease-mediated degradation induced by other RBPs (Chen et al., 1995; Fan and Steitz, 1998b). In one specific case, ELAVL1 promotes neuronal movement by the stabilizing of profilin 1 mRNA (Chen et al., 1995). Similarly, ELAVL1 binding extends the half-life of CX43 mRNA in rat liver epithelial cells (Ale-Agha et al., 2009).

In addition to interacting with the 3′-UTR, ELAVL1 also has multiple effects in other mRNA regions. For example, ELAVL1 can reduce the activity of the internal ribosome entry site (IRES) in the initiation of translation by binding to the 5′-UTR of the mRNA that codes for the insulin like growth factor type 1 receptor (Meng et al., 2005). Conversely, ELAVL1 can stimulate the initiation of translation of X-linked inhibitor of apoptosis (XIAP) mRNA by binding to the IRES in the 5′-UTR of the XIAP mRNA (Durie et al., 2011).

Other members of the ELAVL protein family have not been studied to the extent that ELAVL1 has, but these other family members have been shown to be important in multiple physiological and pathological processes. ELAVL2 (also known as HuB or Hel-N1), ELAVL3 (HuC) and ELAVL4 (HuD) are mainly distributed in neuronal cells (Ripin et al., 2019). ELAVL2 plays a key role in several processes in the early stages of neuronal differentiation, such as cell cycle exit (Hambardzumyan et al., 2009). ELAVL3 has been shown to affect brain function in that low expression levels of ELAVL3 correlated with impaired spatial learning ability of mice and led to the down-regulation of expression of growth associated protein-43 (Quattrone et al., 2001). In addition, the levels of the ELAVL1 transcript and protein in the superior cervical ganglion were found to decrease after the severing of the axon (Deschênes-Furry et al., 2007). These results show that ELAVL2-4 are involved in the development and functioning of the nervous system. Interestingly, however, the functions of these three protein family members go far beyond the brain. They are also essential in the maintenance of physiological functions and the regulation of the occurrence and development of a variety of diseases (Mazan-Mamczarz et al., 2003; Casolaro et al., 2008; Beauchamp et al., 2010; Ahuja et al., 2016; Lee et al., 2018; Zhao et al., 2019).

THE REGULATION OF ELAVL PROTEINS BY NON-RNA MOLECULES

The regulation of ELAVL proteins by non-RNA molecules can be divided into three categories: regulation of protein expression level, regulation of nucleocytoplasmic shuttling, and regulation of the binding of ELAVL proteins to the transcripts in cytoplasm. In gastric tumorigenesis, the activation of AKT serine/threonine kinase promotes the binding of Nuclear Factor-kappa B to the ELAVL promoter, which enhances transcription and the stability of the transcripts (Kang et al., 2008). In addition, the esophageal cancer related gene 2 protein has been shown to increase ubiquitination and degradation of ELAVL1 in the colon cancer derived RKO cell line and the breast cancer-derived MCF7 cell line, but this protein failed to produce similar effects on several non-ubiquitinable mutant forms of ELAVL1 (Lucchesi et al., 2016).

In response to proliferative signals, the phosphorylation of ELAVL1 protein by cyclin-dependent kinase 1 at S202 prevents its translocation to the cytoplasm, resulting in the inhibition of its pro-proliferation and anti-apoptotic effects (Kim et al., 2008). Upon cessation of the external signal, two mechanisms serve to promote relocalization to the cytoplasm. One mechanism involves polyADP-ribosylation of ELAVL1 by poly (ADP-ribose) polymerase 1 (Ke et al., 2017), and a second mechanism is mediated by p38 mitogen-activated protein kinase (Farooq et al., 2009). In another enzyme-controlled mechanism of regulation, sulfhydration by cystathionine γ lyase prevents the homodimerization of ELAVL1, which
ultimately leads to decreases in activity to levels insufficient to increase the expression level of downstream genes in mouse endothelial cells (Bibli et al., 2019).

**INTERACTIONS BETWEEN ELAVL PROTEINS AND VARIOUS CLASSES OF RNA MOLECULES**

**Interactions Between ELAVL Proteins and mRNAs**

One of the main functions of the ELAVL protein family is to regulate the stability and half-life of downstream mRNA. Therefore, their regulatory effects on cells almost entirely depend on the function of downstream mRNAs and the direction of regulation. The most common binding sites where ELAVL proteins interact with mRNAs, AREs in the 3′-UTR, are found in up to 8% of human genome transcripts (Bakheet et al., 2006). These AREs are often regarded as regulatory elements that promote mRNA decay; most RBPs that bind to this region, such as tristetraprolin, butyrate response factor 1, AU-binding factor 1, and KH-type splicing regulatory protein, greatly reduce the half-life of the target RNA (Gherzi et al., 2004; Lykke-Andersen and Wagner, 2005; Gratacós and Brewer, 2010). In most cases, however, the effect of the binding of ELAVL proteins to a downstream mRNA supports stability (Barreau et al., 2005). Previously discovered mRNAs that have been found to bind to the ELAVL family are shown in Supplementary Table 1.

**Interactions Between ELAVL Proteins and ncRNAs**

**Micro RNA (miRNA)**

Various miRNA molecules can bind to the 3′-UTRs of mRNA to decrease the stability of the mRNA. Therefore, the regulation of miRNAs to the ELAVL protein family is mainly reflected in the stability of mRNAs of the latter (Table 1). For example, miR-133, which targets the ELAVL1 mRNA and is sponged by long intergenic non-protein coding RNA, muscle differentiation 1 (linc-MD1), regulates the expression of ELAVL1. The ELAVL1 protein in turn promotes the interaction between linc-MD1 and miR-133 in the early stages of myogenesis (Legnini et al., 2014). Through targeting AREs in ELAVL1 mRNA, miR-155-5p negatively regulates the protein level of ELAVL1 and thus the migration of tumor cells in colorectal cancer (Al-Haidari et al., 2018). In breast cancer, miR-125a inhibited cell proliferation and promoted apoptosis by downregulating ELAVL1 which was highly expressed in cancer cells, and this effect was partially rescued by ELAVL1 overexpression (Guo et al., 2009). In normal human dermal fibroblasts, the overexpression of miR-520d-5p has been shown to down-regulate ELAVL2 and restore cell proliferation; down-regulation of ELAVL2 with small interfering RNA alone achieved the same effect (Ishihara et al., 2014). In mutant motor neurons, decreased expression of miR-375 resulted in increased expression of its downstream targets, which include ELAVL4 as well as p53. These changes promoted the apoptosis and fragility of mutant motor neurons in amyotrophic lateral sclerosis (De Santis et al., 2017).

In turn, ELAVL proteins can regulate miRNAs maturation or co-regulate downstream with miRNAs. In another mode of regulation for miR-199a, hypoxia-induced expression of ELAVL1 prevents the maturation of pre-miR-199a, thereby promoting enhancement of glycolysis through impacts of miR-199a on hexokinase 2 and pyruvate kinase 2 expression in the tumor microenvironment (Zhang et al., 2015). It has been shown that miR-28 targets the mRNA encoding zinc finger protein 36 mRNA in macrophages, but ELAVL1 and miR-28 compete for binding to the 3′-UTR of this mRNA to regulate its stability (Lu et al., 2014). These examples indicate that there is significant crosstalk among RBPs, miRNAs and mRNAs, and that the regulation is not limited to a few isolated cases.

| Member of protein family | miRNA | Interaction and effect | PMID |
|--------------------------|-------|------------------------|------|
| ELAVL1                   | mR-199a | Prevent pre-miR-199a from maturing | 26346275 |
|                          | mR-27  | Competitively bind downstream mRNA | 25533351 |
|                          | mR-133 | Inhibit ELAVL1 mRNA | 24440503 |
|                          | mR-155-5p | | 29471005 |
|                          | mR-125a | | 19875930 |
|                          | mR-519  | | 19088191 |
|                          | mR-582-3p | | 32600329 |
|                          | mR-291b-3p | | 30106126 |
|                          | mR-326  | | 32969928 |
|                          | mR-514a-5p | | 32370736 |
|                          | mR-3127-5p | | 30317610 |
|                          | mR-23c  | | 27964927 |
|                          | mR-146b-5p | | 27166258 |
| ELAVL2                   | mR-520d | Inhibit ELAVL2 mRNA | 25303886 |
| ELAVL4                   | mR-375  | Inhibit ELAVL4 mRNA | 28988989 |
|                          | mR-129-5p | | 32335272 |
Long Non-coding RNA (lncRNA)
The mechanisms by which lncRNAs regulate mRNA activity through the ELAVL protein family, especially ELAVL1, include 1) direct binding to ELAVL1 and promotion of its binding to downstream mRNA, 2) inhibiting of the expression of ELAVL1, 3) stabilizing ELAVL1 protein, 4) direct binding to ELAVL1 and blocking of its binding to downstream mRNA, and 5) promoting the translocation of ELAVL1 from the nucleus to the cytoplasm (Table 2).

First, LINC00707 has been reported as a malignant factor in the progression of lung adenocarcinoma and gastric cancer. LINC00707, which is highly expressed in tumor tissues, has been shown to form a complex with ELAVL1 protein. This complex increases the expression of downstream proteins, such as vav guanine nucleotide exchange factor 3/F11 receptor, and ultimately leads to tumor progression and a poorer tumor prognosis (Xie et al., 2019). In a similar way, lncRNA RMST enhances the binding of ELAVL1 to the mRNA of the target gene DNMT3B, thereby increasing the expression of DNMT3B and global levels of DNA methylation (Peng et al., 2020).

According to multiple reports, lncRNA MAARS, which is positively correlated with the progression of atherosclerosis disease, interacts with ELAVL1 and reduces its cytoplasmic localization, which reduces the apoptosis of macrophages and delays the course of the disease (Simion et al., 2020).

Circular RNA (circRNA)
The class of circRNAs includes closed circular ncRNA molecules that are not easily degraded and have been shown to regulate the progression of various diseases (Li et al., 2015). For example, circRHOBTB3 is expressed at relatively low levels in hepatocellular carcinoma, and it has been reported that over-expression of circRHOBTB3 can lead to degradation of ELAVL1 and thus inhibition of the expression of the ELAVL1 target gene PTBP1 (Chen et al., 2021b). ELAVL1 also interacts competitively with circDL1C1 to negatively regulate the expression of the gene encoding matrix metalloproteinase 1 (Liu et al., 2021); this mechanism occurs

### TABLE 2 | LncRNAs that regulate ELAVL proteins.

| Member of protein family | LncRNA | Interaction and effect | PMID          |
|--------------------------|--------|-----------------------|---------------|
| ELAVL1                   | LINC00707 | Binds to ELAVL1 and stabilizes downstream mRNA | 30502359 |
|                          | RMST    |                       | 31636039 |
|                          | B4GALT1-AS1 |                       | 30182452 |
|                          | MIR100HG |                       | 30102375 |
|                          | lincRNA-UFC1 |                       | 25449213 |
|                          | HMS     |                       | 34302808 |
|                          | IAK136714 |                       | 34015766 |
|                          | AGAP2-AS1 |                       | 33273726 |
|                          | TUG1     |                       | 33047284 |
|                          | TSLNC8   |                       | 32951177 |
|                          | ZEB1-AS1 |                       | 31922280 |
|                          | HOXB-AS1 |                       | 31966581 |
|                          | SNHG7    |                       | 3026094 |
|                          | EGFR-AS1 |                       | 30770799 |
|                          | LINC00707 |                       | 30502359 |
|                          | LINC00324 |                       | 29915327 |
|                          | SPRY4-IT1 |                       | 27853262 |
|                          | APOA4-AS1 |                       | 27131369 |
|                          | lncRNA OCC-1 | Inhibit the expression of ELAVL1 | 29931370 |
|                          | ASB16-AS1 |                       | 3219221 |
|                          | AK058033  |                       | 28035067 |
|                          | FAM83H-AS1 | Stabilize ELAVL1 | 30831080 |
|                          | CAAlnc1   | Blocks ELAVL1 from binding downstream | 30807648 |
|                          | FENDRR    |                       | 31180580 |
|                          | OIP5-AS1  |                       | 26819413 |
|                          | OSER1-AS1 |                       | 3313263 |
|                          | RPSAP52   |                       | 31831098 |
|                          | tie1AS    |                       | 29724820 |
|                          | MALAT1    |                       | 27197265 |
|                          | lncRNA MAARS | Binds to ELAVL1 and promotes its translocation to the cytoplasm | 33262333 |

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in a similar manner with regard to circPPM1F and its target gene PPM1F (Zhang et al., 2020) and circPABPN1 and its target gene ATG16L1 (Li et al., 2020).

The complex between circ-CCND1 and ELAVL1 promotes the expression of the gene encoding cyclin D1 and ultimately leads to the malignant proliferation of laryngeal squamous cell carcinoma (Zang et al., 2020). A similar mechanism has been found in the relationship among CircAGO2/ELAVL/AGO2 (Chen et al., 2019). Further studies have shown that circRNA-mediated positive regulation of downstream mRNAs may be achieved by promoting the cytoplasmic relocation of ELAVL1; thus, circBACH1 binds directly to ELAVL1 and mediates its translocation from the nucleus, thereby increasing its binding to the mRNA encoding p27 (Liu et al., 2020b). At the level of transcription, nuclear-localized circ-HuR derived from ELAVL1 can bind to the transcription factor cellular nucleic acid-binding protein to block this protein from binding to the ELAVL1 promoter, resulting in a decreased expression of ELAVL1 (Yang et al., 2019). In another regulatory mechanism, direct binding of Hsa_circ_00074854 to the ELAVL1 protein improves the stability of the protein, and ultimately promotes hepatocellular carcinoma migration, invasion and epithelial-mesenchymal transition (Wang et al., 2021). The interaction between ncRNA and ELAVL proteins is shown in Figure 2.

**ELAVL PROTEINS IN PATHOLOGICAL AND PHYSIOLOGICAL PROCESSES**

**ELAVL Proteins in Cancers**

ELAVL1

ELAVL1 is indispensable to life. For example, the ELAVL1 gene is expressed during mouse embryonic development and growth...
cycle (Gouble and Morello, 2000), and the knockout of mouse \textit{ELAVL1} leads to hematopoietic failure, loss of intestinal villi, and death within 10 days (Ghosh et al., 2009). Thus, \textit{ELAVL1} protein is necessary in the maintenance of normal life processes. On the other hand, dysregulation of the expression of the \textit{ELAVL1} gene or the activity of the protein can also lead to aberrant cellular growth and cancer. A schematic of the relationships between \textit{ELAVL1} and cancer is shown in Figure 3.

\section*{Colorectal Cancer}

The functions of \textit{ELAVL1} in colorectal cancer have been studied extensively. Importantly, studies have connected \textit{ELAVL1} to cyclooxygenase 2 (COX-2), which has been shown through \textit{in vivo} and \textit{in vitro} studies to be a key factor in the malignant progression of colorectal cancer. On the other hand, dysregulation of the expression of the \textit{ELAVL1} gene or the activity of the protein can also lead to aberrant cellular growth and cancer. A schematic of the relationships between \textit{ELAVL1} and cancer is shown in Figure 3.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure3.png}
\caption{The role of \textit{ELAVL1} in tumors. \textit{ELAVL1} affects tumor biology by either (1) promoting proliferation, (2) inhibiting apoptosis, (3) promoting migration, (4) inducing drug resistance, (5) promoting angiogenesis, or (6) reducing DNA damage. Created with BioRender.com.}
\end{figure}

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Interactions with the cell cycle also explain involvement of \textit{ELAVL1} in colorectal cancer. For example, \textit{ELAVL1} positively regulates the cell division 6 protein, which is highly expressed in colorectal cancer and which drives both the malignant behavior of colorectal cancer and its resistance to oxaliplatin (Cai et al., 2019). It has been reported that in the colorectal carcinoma RKO cell line, the levels of \textit{ELAVL1} in the cytoplasm increase during the late G1, S, and G2 phases of the cell cycle, and it binds to the 3'-UTR of mRNAs encoding cyclins A and B1, resulting in enhanced stability of these mRNAs and increased expression of the proteins, ultimately leading to increased cell proliferation (Wang et al., 2000). In animal experiments, overexpressing \textit{ELAVL1} in RKO cells results in increased tumor sizes upon injection into nude mice (de Silanes et al., 2003).

\section*{Ovarian Cancer}

\textit{ELAVL1} can promote the expression level of COX-2 in ovarian cancer as well as in colorectal cancer, and COX-2 is also positively correlated with poor prognosis and high-grade of ovarian cancer. When the nuclear translocation of \textit{ELAVL1} is suppressed, the expression of COX-2 decreases \textit{in vitro} (Erkinheimo et al., 2003). Accordingly, it has been found that levels of \textit{ELAVL1} in the cytoplasm of cells in ovarian cancer tissues was significantly increased relative to levels in borderline tumors or normal.
ovaries (Denkert et al., 2004). Another interaction with ovarian cancer involves miR-519, which targets the 3′-UTR of ELAVL1 mRNA, inhibiting its translation and slowing cell division of A2780 cells, a human ovarian cancer cell line, in vitro (Abdelmohsen et al., 2008). Also, in A2780 cells, glucose deprivation has been shown to enhance ELAVL1-dependent TUBB3 expression at the mRNA and protein levels, resulting in tumor invasion (Raspaglio et al., 2010).

**Breast Cancer**

ELAVL1 affects the development of breast cancer by regulating the mRNAs associated with a variety of proteins. Accordingly, among familial non-BRCA1/2 breast cancer patients, ELAVL1 can be used as an independent prognostic factor, associated with low survival rate and high tumor malignancy (Heinonen et al., 2007). Mechanistically, ELAVL1 promotes the expression of interleukin (IL)-8, which has clear connections with the progression of breast cancer, via binding to the 3′-UTR of the mRNA encoding IL-1β (Suswam et al., 2005). In addition, the abnormal expression of cyclin E1, Wnt-5a, thrombospondin 1 and the colony stimulating factor receptor is directly related to the increased expression of ELAVL1 in breast cancer models (Guo and Hartley, 2006; Leandersson et al., 2006; Mazan-Mamczarz et al., 2008; Woo et al., 2009). When ELAVL1 is silenced, the programmed death of tumor cells increases and invasion is inhibited (Heinonen et al., 2011). ELAVL1 is also regulated by upstream factors in breast cancer. Levels of miR-125 are negatively correlated with ELAVL1; miR-125 may thus act as an inhibitor of ELAVL1 to decrease translation by binding with its mRNA (Guo et al., 2009).

**Pancreatic Cancer**

The role of ELAVL1 in pancreatic cancer remain controversial. Overexpression of ELAVL1 in pancreatic cancer cells has been shown to increase the sensitivity of patients to gemcitabine treatment. The mechanism of this effect involves the binding of ELAVL1 to and the promotion effect of the mRNA that encodes deoxycytidine kinase whose products can activate gemcitabine (Costantino et al., 2009). In another report, ELAVL1 was also shown to be involved in the apoptosis of pancreatic cancer cells exposed to gemcitabine. ELAVL1 translocates to the cytoplasm after gemcitabine treatment, where it binds to the mRNA of retinoic acid-induced protein 3, which acts as an oncogene, leading to an increase of it at the initial stage of drug treatment (Zhou et al., 2016). Hypoxia in the tumor microenvironment can similarly induce nucleocytoplasmic shuttling of ELAVL1, which then promotes the expression of the PIM1 serine/threonine kinase, which leads to resistance to oxaliplatin (Blanco et al., 2016). In pancreatic ductal adenocarcinoma, ELAVL1 promotes the translation of poly (ADP-ribose) glycohydrolase mRNA, leading to enhanced DNA repair and resistance to the PARP inhibitor olaparib (Chand et al., 2017).

**Other Types of Cancer**

ELAVL1 has been found to play important roles in multiple kinds of tumors. For instance, ELAVL1 has been found to be highly expressed in prostate cancer, and it thus acts as an independent predictor positively correlating with tumor staging and metastasis. ELAVL1 promotes cell proliferation and migration of cells of the prostate cancer lines LNCaP and PC-3 by targeting vascular endothelial growth factors A and C and COX-2 (Barbisan et al., 2009; Mitsuari et al., 2016).

In hepatocellular carcinoma cells, the highly expressed lincRNA-UFC1 directly binds to ELAVL1, leading to an increase of β-catenin mRNA and protein and finally increased cell proliferation and decreased apoptosis (Cao et al., 2015). Similarly, lsa_circ_0074854 promotes the migration and invasion of hepatocellular carcinoma cells by stabilizing ELAVL1 (Wang et al., 2021). On another hand, ELAVL1 binds pre-miRNA-199a to prevent its maturation, leading to enhanced glycolytic metabolism in hepatocellular carcinoma cells in response to hypoxia (Zhang et al., 2015).

In glioblastoma multiforme and adjacent tissues, high expression of ELAVL1 can also be detected (Nabors et al., 2001). In glioblastoma, pyruvate kinase M2, which is up-regulated, binds to ELAVL1 and promotes its cytoplasmic localization, prompting tumor cells to enter a dividing state and promoting cell growth (Mukherjee et al., 2016). In a nude mouse model of glioblastoma, knockdown of ELAVL1 reduced tumor growth and proliferation, and prolonged survival time (Wang et al., 2019b).

Generally speaking, ELAVL1 often appears as a malignant factor. On the one hand, it is indispensable in life activities. On the other hand, the tumorigenic effects of high expression of ELAVL1 acts as an important contributor to the progression and invasion of many types of tumor through various pathways. Therefore, ELAVL1 may be a potential drug target with universal applicability.

**ELAVL2-4**

The three other family members, ELAVL2, ELAVL3 and ELAVL4, initially received much attention as neuroendocrine markers for small cell lung cancer (SCLC) (King, 1997; D’Alessandro et al., 2008). Among them, ELAVL4 received the most attention in SCLC, because it was found to be expressed in 100% of SCLC cells and more than 50% of neuroblastoma cells, and treatment targeting ELAVL4 can reduce tumor progression in nude mouse models (Ohwada et al., 1999; Ehrlich et al., 2014). As the antigen target of autoreactive CD4+ T cells, ELAVL4 may directly participate in cell-mediated anti-tumor immunity and nervous system damage (Benyahia et al., 1999).

At the level of post-transcriptional regulation, ELAVL4 regulates RNA as an RBP, but in tumorigenic neuroblasts, ELAVL4 also takes part in the nuclear processing and stability of the pre-mRNA of the proto-oncogenic transcription factor N-myc (Lazarova et al., 1999). ELAVL4 has also been shown to interact with both the 3′-UTR and 5′-UTR regions of the p27 mRNA to promote its translation leading to tumor suppression, but ELAVL4 and p27 levels are both reduced in pancreatic neuroendocrine tumors (Kim et al., 2018). Outside of SCLC, ELAVL2 has been shown to be an independent risk factor in esophageal squamous cell carcinoma, and it increases the resistance of these tumor cells to paclitaxel and cisplatin (Zhao et al., 2019).
There are also notable cancer-related interactions between members of the ELAVL family. A combination of ELAVL2 and ELAVL1 has been shown to localize to the nucleus and to be indispensable in the activation of several proto-oncogenes, including v-fos, v-ets, and v-myc (Hatanaka et al., 2019). Also, by binding with a structure containing an AU-rich sequence, ELAVL2 and ELAVL4 together inhibit the assembly of the core complex of telomerase to reduce its activity and cell growth in human neuroblastoma cells; notably, the activity of this complex antagonizes the function of ELAVL1 (Cheng et al., 2021). Surprisingly, considering the importance of the other ELAVL family members, few reports link ELAVL3 to tumor development or progression.

**ELAVL Proteins in Disorders of the Nervous System**

The ELAVL protein family was originally best known for its associations with the nervous system (Akamatsu et al., 1999). In the development of the neocortex, the deletion of ELAVL1 reduces the phosphorylation of eIF2a and eEF2 and the formation of polysomes, ultimately leading to the mis-localization of mRNAs. The lack of ELAVL1 reduces the stability of PFN1 mRNA and affects actin polymerization, resulting in the mis-localization of neurons in the neocortex (Kraushar et al., 2014; Zhao et al., 2020a). It also participates in cellular metabolism and protection from oxidation-induced neurodegeneration (Skliros et al., 2015).

With regard to various disease states, ELAVL1 has either protective or damaging effects, depending on the circumstances. In spinal muscle atrophy, ELAVL1 stabilizes survival motor neuron transcripts, which leads to accumulation of the protein products, thus alleviating the loss of alpha motor neurons that otherwise lead to progressive muscle atrophy (Farooq et al., 2009). In the occurrence and progress of neurodegenerative diseases, including age-related macular degeneration, ELAVL1 promotes the early elevation and accumulation of P62 in response to the early activation of autophagy, clearing protein multimers and alleviating neurodegenerative effects (Marchesi et al., 20182018).

On the other hand, ELAVL1 has been found to play deleterious roles in Huntington’s disease and amyotrophic lateral sclerosis. In Huntington’s disease, which is caused by mutations in the HTT gene and abnormal accumulation of the HTT protein, the HTT protein itself induces ELAVL1 to stabilize HTT mRNA, forming a positive feedback loop (Zhao et al., 2020b). Moreover, inhibition of ELAVL1 has been shown to block the chronic activation of microglia in amyotrophic lateral sclerosis and to delay the course of this disease (Matsye et al., 2017).

In neurons, ELAVL2, ELAVL3, and ELAVL4 function in stages. ELAVL2 protein is expressed in early neuron progenitor cells through to mature neurons, while ELAVL3 and 4 are expressed later than ELAVL2 and function mainly in cortical neuron development (Yano et al., 2016). Multiple studies have linked ELAVL4 to neuron development and plasticity (Bronicki et al., 2012; Loffreda et al., 2020). ELAVL4 is engaged in stabilization of tau microtubule-associated protein transcripts and maintains axon development in neuronal cells. Accordingly, the inhibition of ELAVL4 results in the cessation of axonal growth (Aranda-Abreu et al., 1999; Fukao et al., 2009; Hao le et al., 2017), and a deficiency of ELAVL4 in mice leads to transient impaired cranial nerve development during the embryonic period in vivo (Akamatsu et al., 2005).

Similar to ELAVL1, ELAVL4 is indispensable for establishing neocortex and hippocampal circuits and maintaining the function of these circuits (DeBoer et al., 2014). Furthermore, in the adult subventricular zone neural stem and progenitor cells, ELAVL4 promotes neuronal differentiation through special AT-rich sequence-binding protein 1 (SATB1). A lack of SATB1 affects the maturation of neuronal stem cells, and the overexpression of SATB1 in ELAVL4-suppressed cells can restore the neuronal differentiation phenotype (Wang et al., 2015). ELAVL2 promotes the exit from the cell cycle during the neuronal stem cell maturation, and overexpression of ELAVL2 restricts the proliferation of neuronal stem cells (Hambardzumyan et al., 2009). For ELAVL3, a low level of ELAVL3 leads to the impairment of spatial learning ability of mice with lowered expression of growth-associated protein 43 (Quattrone et al., 2001).

**ELAVL Proteins in Other Physiological and Pathological Process**

In addition to cancer and processes involving the nervous system, the ELAVL protein family is also involved in muscle differentiation (Beauchamp et al., 2010), aging (Lee et al., 2018), inflammation (Casolaro et al., 2008), stress events (Mazan-Mamczarz et al., 2003; Ahuja et al., 2016) and other processes. Figure 4 shows how tumors and other different diseases interact with ELAVL proteins.

The impact on muscle differentiation involves a novel proteolytic cleavage of ELAVL1. When transferred to the cytoplasm in myoblasts, some ELAVL1 is cleaved into two fragments, cleavage products (CP) 1 and 2, of sizes 24 and 8 kDa, respectively. CP1 forms a complex with ELAVL1 import factor transportin-2 (TRN2), allowing uncleaved ELAVL1 to remain in the cytoplasm. The other fragment, CP2, promotes myogenesis (Beauchamp et al., 2010).

The known impact of ELAVL1 on aging involves interactions with the telomeric protein TIN2. ELAVL1 binding destabilizes TIN2 mRNA to decay quickly. Therefore, when ELAVL1 is inhibited, the expression of TIN2 protein in the mitochondria are increased. These factors correlate with increased levels of ROS, ultimately leading to cell senescence (Lee et al., 2018).

Inflammatory stimuli lead to poly ADP-ribosylation of D226 of ELAVL1. Modified ELAVL1 oligomerizes in the presence of PARP1, resulting in the protection of pro-inflammatory mRNA from degradation induced by miRNA and other factors. Therefore, treatments targeting ELAVL1 alleviate the lipopolysaccharide-induced accumulation of inflammatory cells in the airways of mice (Ke et al., 2021). In another inflammatory disease, pterygium, the activation of matrix metalloproteinase 9 by ELAVL1 amplifies the pro-inflammatory effect of IL-1β (Cui et al. 2021).
et al., 2020). The combination of ELAVL1 and matrix metalloproteinase 9 also appears in the inflammatory infiltration of cardiomyocytes in acute myocardial infarction. IL-10 can inhibit this combined effect to alleviate fibrosis and inflammation, and ultimately reduce damage to left ventricular function (Krishnamurthy et al., 2009).

Under the influence of different stressors, the function of ELAVL1 changes accordingly. Low-level UV irradiation induces the translocation of ELAVL1 to the cytoplasm, where it interacts with and preserves transcription products by binding with them after the formation of DNA damage. At the same time, the transcription process is inhibited to prevent the generation of false transcripts. In this mode, ELAVL1 is beneficial to cell survival (Mazan-Mamczarz et al., 2003). On the other hand, after ionizing radiation, ELAVL1 is separated from almost all mRNAs, including proliferation-related and apoptosis-related proteins. While this mechanism is different from that associated with UV irradiation, it similarly contributes to a better survival outcome for cells (Masuda et al., 2011). However, when cells are subjected to high pressure stress, ELAVL1 is translocated to the cytoplasm and where it is cleaved by caspases at A226, and this action amplifies apoptotic signals (Mazroui et al., 2008).

**INHIBITORS OF ELAVL1**

Research on the inhibitors of ELAVL proteins has mainly focused on ELAVL1. In view of the positive regulation of ELAVL1 in tumor promotion, the research and development of inhibitors is of significance. At present, the effects of inhibitors on ELAVL1 are mainly focused in four directions: inhibiting its nucleocytoplasmic trafficking, blocking its binding to mRNA, suppressing its dimerization/multimerization and downregulating its expression. As shown in Figure 5, MS-444 (Meisner et al., 2007), dehydromutactin (Meisner et al., 2007), okicenone (Meisner et al., 2007), eltrombopag (Zhu et al., 2020) and SRI-42127 (Filippova et al., 2021) inhibit the dimerization/multimerization of ELAVL1; 5-aza-2′-deoxycytidine (AZA) (Hostetter et al., 2008), trichostatin A (TSA) (Hostetter et al., 2008), pyrvinium pamoate (Guo et al., 2016) and Rottlerin (Latorre et al., 2012) inhibit ELAVL1’s nucleocytoplasmic trafficking; Dihydrotanshinone-I (Lal et al., 2017), azaphilone-9 (AZA-9) (Kaur et al., 2017), quercetin (Chae et al., 2009), b-40 (Chae et al., 2009), suramin (Kakuguchi et al., 2018), KH-3 (Wu et al., 2020) and CMLD1 (Wu et al., 2015) block ELAVL1’s binding to mRNA; CMLD2 downregulates ELAVL1’s expression (Muralidharan et al., 2017) and blocks its binding to mRNA (Wu et al., 2015). Among these inhibitors, MS-444, dehydromutactin, okicenone, SRI-42127, AZA-9, b-40, KH-3, CMLD1 and CMLD2 are specific inhibitors of ELAVL1, while others are not. For example, eltrombopag often acts as a thrombopoietin (TPO) receptor agonist (Bussel et al., 2019), AZA as a DNA methyltransferase inhibitor (Song et al., 2022) and TSA as a histone deacetylase inhibitor (He et al., 2022). Pyrvinium pamoate (Faheem et al., 2022), Rottlerin (Hufnagel et al., 2009), dihydrotanshinone-I (Sun et al., 2022), quercetin (Zaragozá et al., 2022) and suramin (Zhang et al., 2022) all have effects on other physiological or pathological processes.
CONCLUSION AND PERSPECTIVE

This review summarizes the role of ELAVL proteins in various pathophysiological processes and in regulating mRNA and ncRNA. Given the ubiquity of ELAVL proteins existence and their role in a variety of diseases, it is logical to develop innovative small molecules. Based on the interaction mechanism between ncRNA and ELAVL proteins, the development of ncRNA analogs to promote the degradation of ELAVL proteins or inhibit the translation of their mRNAs is worth discussing. Developing chemically inactive analogs of ELAVL proteins to interfere with their synergy or competition with ncRNA in a competitive manner may also provide a new perspective to reduce the functionality of the protein family. Notably, although the ELAVL proteins have promising potential as a therapeutic target, many questions still need to be further explored. Interfering with ELAVL proteins seems to be a new strategy; however, considering that they are an integral part of life activities and interact with too many RNA molecules, whether their intervention will cause other unexpected side effects needs to be handled carefully. Is it better to use it alone or in combination with other drugs? According to previous reports, inhibition of ELAVL1 sensitized tumors to treatment with platinum-based drugs, including oxaliplatin and cisplatin (Young et al., 2009). What about drugs other than platinum-based drugs? In addition, considering ELAVL2-4 participating in many pathological processes and the similarity of the structure between ELAVL2-4 and ELAVL1, substantial study is imminent to fill the lacunae in the development of ELAVL2-4 inhibitors.

AUTHOR CONTRIBUTIONS

HJC and DDZ collected literatures, prepared figures and tables, drafted the manuscript and edited the manuscript. YZY helped to arrange the manuscript. LHY, XYH and LXW conceived the idea and reviewed the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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GLOSSARY

AGAP2 ArfGAP with GTPase domain, ankyrin repeat and PH domain 2
AGAP2-AS1 AGAP2 antisense RNA 1
AGO2 Argonaute 2
APOA4-AS Rho GTPase activating protein 21
ARE AU-rich element
ASB16 ankyrin repeat and SOCS box containing 16
ASB16-AS1 ASB16 antisense RNA 1
ATG16L1 Autophagy Related 16 Like 1
B4GALT1-AS1 B4GALT1 Antisense RNA 1
BRCA breast cancer;
CAAlnc1 cachexia-related anti-adipogenesis IncRNA 1
CircAGO2 circular RNA Argonaute 2
circBACH1 circular RNA BTB Domain and CNC Homolog 1
circ-CCND1 circular RNA Cyclin D1
circDLC1 circular RNA DLC1
circ-HuR circular RNA ELAV like RNA Binding Protein 1
circRHOBTB3 circular RNA RHOBTB3
circRNA circular RNA
COX-2 cyclooxygenase 2
CP cleavage products
CX43 Connexin 43
DNMT3B DNA methyltransferase 3B
eEF2 Eukaryotic Translation Elongation Fa
EGFR epidermal growth factor receptor
EGFR-AS1 EGFR antisense RNA 1
eIF2a Eukaryotic Translation Initiation Factor 2A
ELAVL proteins Embryonic lethal abnormal vision-like proteins
FAM83H-AS1 family with sequence similarity 83 member H antisense RNA 1
FENDRR FOXF1 adjacent non-coding developmental regulatory RNA
HCT116 human colon cancer cells 116
Hel-N1 human elav-like neuronal protein 1
HMS HOXC10 mRNA stabilizing factor
HOXB homeobox B cluster
HOXB-AS1 HOXB cluster antisense RNA 1
HTT Huntingtin
HuB human antigen B
HuC human antigen C
HuD human antigen D
HuR human antigen R
IL interleukin
IRES internal ribosome entry site
lincRNA-UFC1 long intergenic noncoding RNA UFC1
IncRNA Long non-coding RNA
MAAARS Macrophage-Associated Atherosclerosis
MALAT1 metastasis associated lung adenocarcinoma transcript 1
MD1 muscle differentiation 1
MIR100HG mir-100-let-7a-2-mir-125b-1 cluster host gene
miRNA micro RNA
mRNA message RNA
ncRNA non-coding RNA
NF-κB Nuclear Factor-kappa B
OCC-1 Overexpressed in colon carcinoma-1
OIP5 Opa interacting protein 5
OIP5-AS1 OIP5 antisense RNA 1
OSER1 oxidative stress responsive serine rich 1
OSER1-AS1 OSER1 antisense RNA 1
p27 protein 27
p53 protein 53
P62 protein 62
PARP1 poly(ADP-ribose) polymerase 1
PFN1 profilin 1
PIM1 Pim-1 Proto-Oncogene, Serine/Threonine Kinase
PPM1F Protein Phosphatase, Mg2+/Mn2+ Dependent 1F
PTBP1 Polyypyrimidine Tract Binding Protein 1
RBP RNA-binding protein
RMST habdomyosarcoma 2-Associated Transcript
ROS reactive oxygen species
RPSAP52 ribosomal protein SA pseudogene 52
RRM RNA recognition motif
SATB1 sequence-binding protein 1
SCLC small cell lung cancer
SNHG7 small nucleolar RNA host gene 7
SPRY4 sprouty RTK signaling antagonist 4
SPRY4-IT1 SPRY4 intronic transcript 1
tie1AS tie1 locus-tie1 antisense
TIN2 TRF1-interacting nuclear protein 2
TRN2 transportin-2
TSLNC8 Tumor suppressor long noncoding RNA on chromosome 8p12
TUBB3 Tubulin Beta 3 Class III
TUG1 aurine up-regulated 1
UTR untranslated region
UV Ultraviolet Rays
Wnt-5a Wnt Family Member 5A
XIAP X-linked inhibitor of apoptosis
ZEB1 zinc finger E-box binding homeobox 1
ZEB1-AS1 ZEB1 antisense RNA 1.