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REVIEW

ELAV/Hu RNA-binding protein family: key regulators in neurological disorders, cancer, and other diseases

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ABSTRACT

The ELAV/Hu family represents a crucial group of RNA-binding proteins predominantly expressed in neurons, playing significant roles in mRNA transcription and translation. These proteins bind to AU-rich elements in transcripts to regulate the expression of cytokines, growth factors, and the development and maintenance of neurons. Elav-like RNA-binding proteins exhibit remarkable molecular weight conservation across different species, highlighting their evolutionary conservation. Although these proteins are widely expressed in the nervous system and other cell types, variations in the DNA sequences of the four Elav proteins contribute to their distinct roles in neurological disorders, cancer, and other Diseases . Elavl1, a ubiquitously expressed family member, is integral to processes such as cell growth, ageing, tumorigenesis, and inflammatory diseases. Elavl2, primarily expressed in the nervous and reproductive systems, is critical for central nervous system and retinal development; its dysregulation has been implicated in neurodevelopmental disorders such as autism. Both Elavl3 and Elavl4 are restricted to the nervous system and are involved in neuronal differentiation and excitability. Elavl3 is essential for cerebellar function and has been associated with epilepsy, while Elavl4 is linked to neurodegenerative diseases, including Parkinson's and Alzheimer's diseases. This paper provides a comprehensive review of the ELAV/Hu family's role in nervous system development, neurological disorders, cancer, and other diseases.

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Introduction

Mammalian gene expression is a complex and tightly regulated process. Beyond transcription, mRNA processing, transport, stability, and translation are crucial for regulating gene expression in the nervous system. These post-transcriptional processes are regulated by the interaction of certain RNA-binding proteins (RBPs) with specific sequences in target mRNAs, while others are unconventional RBPs (ucRBPs) that lack known RNA-binding domains (RBDs) and often exhibit no sequence specificity [1]. (Figure 1C) RBPs, which bind to single- or double-stranded RNA, have selective affinity for various RNAs and regulate multiple RNA functions, influencing cell fate [2,3]. They protect target RNAs from pre-mRNA transcription in the nucleus through nuclear export until translation is completed in the cytoplasm [4]. Through numerous in vivo and in vitro studies, over 1,000 RBPs with distinct functions have been identified in humans and mice [5]. RBPs participate in processes including mRNA processing and maturation, coordination and stabilization of protein complexes, alternative splicing, polyadenylation, silencing, degradation of mature mRNA, as well as intracellular transport, localization, and stabilization [6,7]. (Figure 2) Given their involvement in numerous post-transcriptional mechanisms, RBP dysfunction may contribute to a variety of diseases, such as cardiovascular diseases, immune disorders, cancer, and neurodegenerative diseases [8,9]. Among them, RBPs are very closely linked to central nervous system diseases, including Alzheimer's disease, Parkinson's disease, autism, and schizophrenia [10–12]. (Figure 3)

In the nervous system, alternative splicing is highly prevalent, and RBPs help protect mRNA from premature translation and degradation during its transport from neurons to dendrites and axons [13]. One of the most extensively studied neuronal RBPs is the embryonic lethal abnormal visual system ELAV/Hu protein, which plays a key role in co-transcriptional regulation of pre-mRNA [14,15]. The protein family was first identified in *Drosophila* [16], where it encodes three neural-specific RBPs: Elav (Embryonic Lethal Abnormal Vision), Rbp9 (RNA-binding protein 9), and Fne (Found in neurons). These proteins are involved in neuron development and function in *Drosophila*, and mutations during embryonic development can cause embryonic lethality and visual defect [17]. ELAV/Hu proteins were later identified in humans as tumour-specific antigens in paraneoplastic neuropathy,

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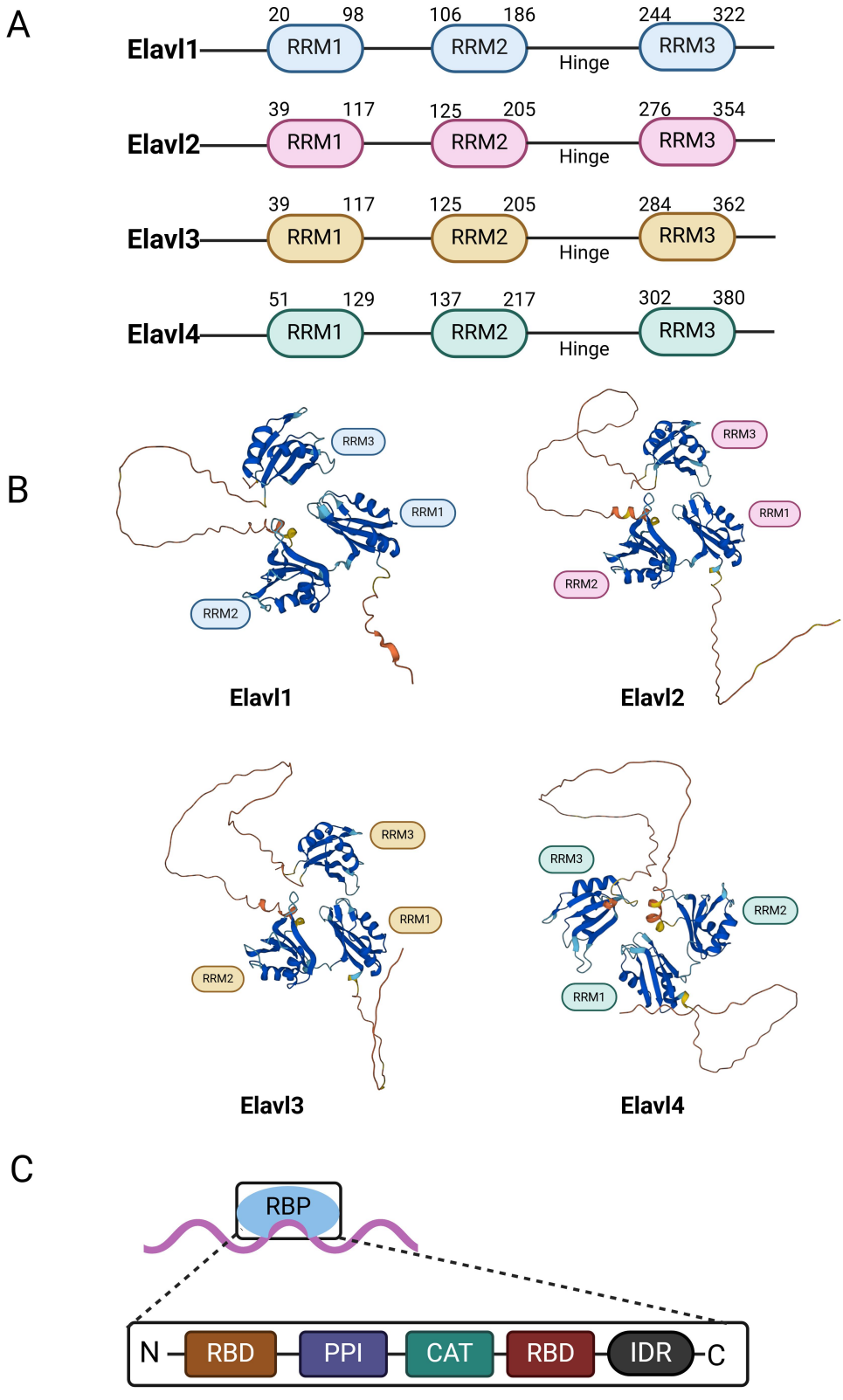

Figure 1. The structure of ELAV/Hu RNA-binding protein (A) A schematic of the four human ELAV proteins, including the three RNA recognition motifs (RRM) and hinge region. (B) AlphaFold predicted protein structures for Elavl1 and Elavl4. The general organization of the protein is the same with three core RRM domains and a disordered hinge domain. (C) General modular structure of RNA-binding proteins. The binding of multiple RNA-binding proteins (RBPs) onto the same target RNA dictates the metabolic fate of the transcript. RBPs display a modular architecture, as they may be endowed with several domains. RBPs bind to the specific transcript through one or more RNA-binding domains (RBDs). Protein-protein interaction (PPI) and catalytic (CAT) domains mediate the binding to other partner proteins and the activity of the RBPs, respectively. In addition, several RBPs contain intrinsically-disordered regions (IDRs), which generally lack a defined three-dimensional structure. The number and type of each domain varies greatly among RBPs. A large number and combination of post-translational modifications (PTMs) further increases the structural and functional complexity of RNA-binding proteins. Figure 1 created with BioRender.com.

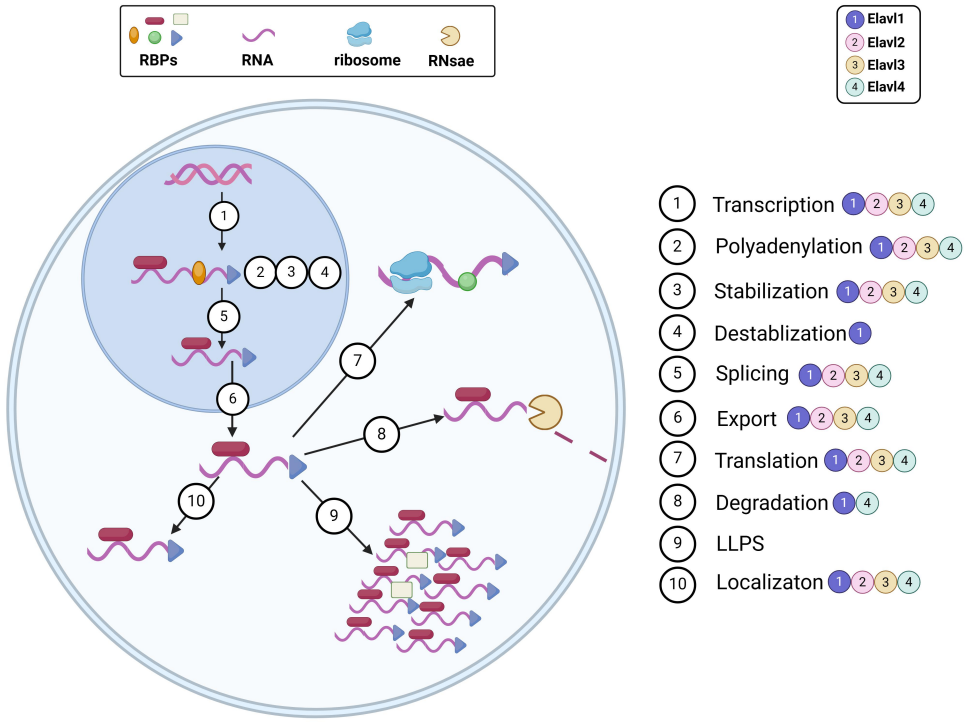

Figure 2. The function of ELAV/Hu RNA-binding protein RNA-binding proteins-mediated modulation of RNA metabolism. The schematic picture describes some of the processes through which RNA-binding proteins (RBPs) influence RNA biology inside the nucleus and the cytoplasm of a cell. These processes include (but are not limited to): transcription, polyadenylation, stabilization, RNA splicing, export, cellular localization, translation, degradation, and liquid-liquid phase separation (LLPS). Figure 2 created with BioRender.com.

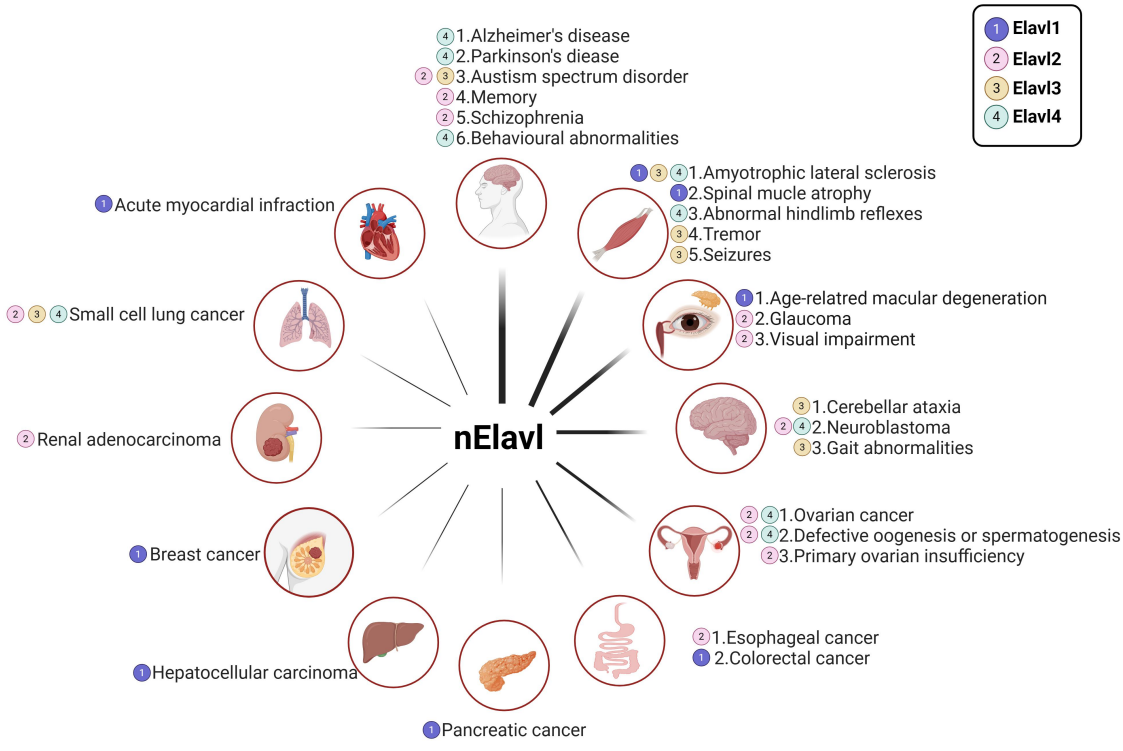

Figure 3. The relationship between ELAV/Hu RNA binding protein and disease. Diseases or pathophysiological processes related to ELAV proteins. Diseases related to ELAV proteins are included in the figure. Colors indicate which of the nELAV genes the phenotype or disease has been associated with Elavl1 (purple), Elavl2 (pink), Elavl3 (yellow), Elavl4 (green). Figure 3 created with BioRender.com.

particularly in lung cancer patients [18]. These antigens can trigger the production of anti-Hu antibodies, which cross the blood-brain barrier and cause neurological disorders characterized by dementia and spinal cord lesions [19]. Moreover, Hu proteins in humans show high homology to *Drosophila* Elav proteins. (Figure 1B) The four members of the Hu family – HuR, HuB, HuC, and HuD – correspond to Elavl1, Elavl2, Elavl3, and Elavl4 respectively. Elavl2 through Elavl4, also known as neuronal Elav proteins, are predominantly expressed in neurons, with high sequence homology (70–85%) among them [20–24]. In humans and mice, the ELAV family comprises four members – Elavl1 (HuR, ~36 kDa), Elavl2 (HuB, ~39 kDa), Elavl3 (HuC, ~39 kDa), and Elavl4 (HuD, ~42 kDa) [25]. In contrast, *Drosophila melanogaster* encodes a single Elav gene (~50 kDa) [26], while in *Caenorhabditis elegans* the homologs range from 40 to 50 kDa [27]. *Zebrafish* and *Xenopus laevis* exhibit Elav protein sizes similar to those in mammals (approximately 36–42 kDa) [28,29]. This remarkable conservation in molecular weight across species underscores the evolutionary importance of ELAV-like RNA-binding proteins [30]. Phylogenetic studies reveal that HuR, HuB, HuC, and HuD have followed distinct evolutionary trajectories, acquiring specialized functions in both neural and non-neural contexts. Moreover, comparative analyses in insects (e.g. Drosophila ELAV) and mammals support the notion that, following duplication, ancestral ELAV genes evolved tissue-specific regulatory elements that facilitated their functional specialization [31,32].

In mammals, ELAV/Hu proteins (Elavl1, Elavl2, Elavl3, and Elavl4) show dynamic localization, typically found in the nucleus or cytoplasm, depending on cell type, differentiation state, and external conditions. For example, HuR (Elavl1) is mainly nuclear but can move to the cytoplasm under stress, while HuD (Elavl4) is predominantly cytoplasmic, especially in neuronal axons and synapses. This flexible distribution highlights their diverse roles in mRNA regulation [33–36]. The Elav-like proteins contain three highly conserved RNA recognition motifs (RRM). (Figure 1A)The two tandem RRMs at the n-terminus are separated by a basic segment from the third RRMs and connected to the c-terminal polyadenylation recognition site through a variable sequence containing cis-acting elements for nuclear-cytoplasmic shuttling [37–39]. The polyadenylation site exhibits a strong affinity for the AU-rich elements (AREs) in the 3'-UTR of target mRNAs, where ELAV/Hu proteins bind to regulate the expression of cytokines, growth factors, and proteins involved in neuronal differentiation and maintenance [40–44]. Binding at this site stabilizes the Elavl-mRNA complex by preventing exonuclease-mediated degradation or by facilitating interactions with other RNA-stabilizing factors [23,45]. In addition, the third RRM mediates binding to the poly (A) tail of mRNA, which proves that Elav-like proteins can bind to both AU-rich elements and poly (A) tails [44,46]. Beyond their role in neuronal development and maintenance, the co-transcriptional regulatory functions of the ELAV/Hu protein family are increasingly linked to a growing number of diseases [47–50]. (Figure 3) A deeper understanding of these proteins will offer insights into their mechanisms in nervous system development, the pathogenesis of neurological disorders, cancer, and other diseases.

The structure and function of Elavl1/HuR protein

Elavl1 was first successfully cloned and characterized in 1996 as an RNA-binding protein that is widely expressed in various tissues, including adipose tissue, spleen, intestines, and testes [41]. It plays a critical role in regulating cell proliferation and differentiation and is essential for normal embryonic development and survival. Studies in mouse models have demonstrated that *Elavl1* knockout leads to embryonic lethality during the second trimester, highlighting its necessity for normal embryonic survival and development [51]. Under physiological conditions, the *Elavl1* gene in mice produces three mRNA isoforms with different 3′ untranslated region (UTR) lengths. The most abundant form is the 2.4 kb mRNA, which is widely expressed, while the 1.5 kb mRNA is testis-specific and a 6.0 kb neuron-specific mRNA is expressed in the brain [52]. These isoforms can interconvert under different conditions to fulfil distinct functions [53–57]. *Elavl1* predominantly resides in the nucleus, where it regulates splicing [58–61] and polyadenylation [62]. Normally, AU-rich elements (AREs) destabilize mRNA by accelerating deadenylation, but Elavl1 competes with these elements, thereby increasing mRNA stability and translation [63,64]. Elavl1 is also involved in various physiological processes, including cellular senescence [65], tumour growth [36], stress responses and apoptosis [66], neuroinflammation [67], and motor neuron injury [68]. By regulating target mRNA, Elavl1 influences the cellular response to different stimuli, such as stress, proliferation, differentiation, apoptosis, ageing, immunity and inflammation [40,69,70]. In the central nervous system, Elavl1 not only supports normal neural development but is also closely associated with neuroinflammation and motor neuron injury [71]. Elavl1 is implicated in the activation of astrocytes and microglia, and is particularly overexpressed in the spinal cord microglia of humans and mice with amyotrophic lateral sclerosis (ALS) [72]. In neuron-specific *Elavl1* knockout models, increased expression of activated caspase-3 in motor neurons leads to motor neuron injury [73–77].

In addition to its role in the nervous system, Elavl1 also plays a crucial role in inflammation and cancer. In the cytoplasm, Elavl1 plays a key role in cell and tissue differentiation by regulating mRNAs involved in inflammation and regeneration [67,69]. Inflammatory cytokines, such as interleukin-6, interleukin-8, transforming growth factor-β, C-reactive protein (CRP), tumour necrosis factor-α, and complement components, are stabilized and expressed in various immune cells, including fibroblasts, macrophages, and T cells, through Elavl1-mediated regulation [78–81]. In inflammatory diseases such as vasculitis, Elavl1 promotes the inflammatory response [68]. Moreover, inhibition of *Elavl1* significantly alleviates motor dysfunction and hyperalgesia in models of autoimmune encephalomyelitis. Elavl1 also plays a role in chronic inflammatory diseases, such as pancreatitis [82], rheumatoid arthritis [83] and asthma [84]. Elavl1 is the most extensively studied member of the Elav protein family in cancer research. It is expressed in various cancers, including lung cancer, neuroblastoma, small cell lung cancer, prostate cancer, and ovarian cancer [36], and it promotes tumour formation, cell proliferation, and metastasis. Recent studies have shown that

Elavl1 interacts with *IDH1* to regulate metabolic activity in pancreatic ductal adenocarcinoma [85]. Evidence suggests that *Elavl1* acts as an oncogene, enhancing the transcriptional activity of target mRNAs and promoting cancer hallmarks, such as sustained proliferative signalling, evasion of growth suppression, invasion and metastasis, induction of angiogenesis, replicative immortality, inhibition of cell death, and promotion of tumour-related inflammation and immune evasion [86–93]. The expression of *Elavl1* is an important prognostic marker for benign and malignant tumours. For example, in ductal breast carcinoma, increased cytoplasmic *Elavl1* is associated with poor differentiation, larger tumour size, lower survival rates, and resistance to radiotherapy and chemotherapy [94,95]. In meningioma, Elavl1 serves as a prognostic marker. Currently, targeting *Elavl1* is considered a promising therapeutic strategy in cancer treatment. Silencing *Elavl1* is being explored as an adjunct target for chemotherapy in pancreatic cancer [96]. Additionally, IL-10 reduces the expression of inflammatory cytokines post-transcriptionally by inhibiting *Elavl1* expression. Inhibition of *Elavl1* has also been shown to enhance the sensitivity of breast and colon cancer cells to low-dose radiotherapy by approximately two-fold [95].

In the visual system, *Elavl1* moves from the nucleus to the cytoplasm in response to oxidative stress, particularly in the human trabecular meshwork, where it regulates intraocular pressure. This process is linked to glaucoma by controlling stress-response proteins like Hsp70 and p53 [97,98]. Reduced cytoplasmic Elavl1 in glaucoma models and human samples leads to lower levels of these proteins, contributing to glaucoma development. Elavl1 also plays a role in diabetic retinopathy by stabilizing mRNAs of TNF-α and VEGF, promoting disease progression [99]. In age-related macular degeneration (AMD), Elavl1 worsens retinal pigment epithelial cell dysfunction, leading to drusen formation. Inhibiting *Elavl1* expression has shown promise in slowing diabetic retinopathy, making it a potential therapeutic target for retinal diseases [99].

Neuronal ELAVs (neuronal Elav-like proteins, nELAVs) protein structure and function

The nElavls family of proteins consists of three members: Elavl*2*, Elavl3, and Elavl4, which serve as molecular markers specific to neurons [100]. These proteins bind to target mRNAs, regulating processes such as RNA nuclear export, alternative splicing, polyadenylation, and translation, playing critical roles in neuronal development and maintenance [14]. Research in zebrafish demonstrates that nElavls are expressed in early-generated neurons within the retina, such as amacrine cells (ACs) and retinal ganglion cells (RGCs). Additionally, nELAVs expression has been observed in post-mitotic fibroblasts of the lens in rats and mice [101]. Increasing evidence suggests that nELAVs are highly enriched in neurons and play significant roles in neurodegenerative diseases, including fragile X syndrome [102], Parkinson's disease [103], Huntington's disease [104], and Alzheimer's disease [105,106]. nELAVs promote neuronal development by facilitating central nervous system plasticity, and supporting peripheral nerve regeneration. They also enhance axonal growth, and nerve recovery following injury [20,24,40,49,107,108]. Borgonetti et al. [40] Studies indicate that *Elavl2*, *Elavl3*, and *Elavl4* in the mammalian cerebral cortex exhibit distinct temporal and spatial expression patterns, suggesting specialized roles in neuronal development beyond their shared functions, with *Elavl2* and *Elavl4* displaying similar patterns that differ slightly from *Elavl3* [109,110].

The structure and function of Elavl2 protein

Elavl*2* protein was initially detected in neuronal progenitor cells of the developing embryonic cortical layer, followed by the expression of Elavl4 and Elavl3 proteins. It was specifically expressed in the progenitor cells of the mouse telencephalon, with expression levels increasing rapidly from embryonic day E16.5. At the same time, the neuronal progenitor cell marker Tbr2 was co-expressed with Elavl2, suggesting that Elavl*2* may play a role in the differentiation of neuronal progenitor cells in the brain [111]. Additionally, Elavl2 is closely associated with the 3′UTR of *Foxg1*, promoting its expression by counteracting the inhibitory effect of miR-9 and thereby regulating the differentiation of embryonic forebrain progenitor cells [112]. Previous studies revealed that *Elavl2* begins to express in the mouse retina at embryonic day E12.5 and continues long after birth, specifically in amacrine cells (ACs), retinal ganglion cells (RGCs), and horizontal cells. In an *Elavl2*-knockout mouse model, Elavl2 was found to play a critical role in the generation and differentiation of retinal ACs. *Elavl2* deficiency led to the down-regulation of transcription factors Nr4a2, Barhl2, and Neurod1, reducing the production of GABAergic and glycinergic transmitters in ACs and ultimately impairing visual function and acuity. Moreover, Elavl2 interacts with GABAB receptors at both RNA and protein levels, participating in signal transduction [109,113] ELAVl2 has also been implicated in neurological disorders, including schizophrenia and autism. Genome-wide association studies (GWAS) have identified *ELAVl2* as a key gene in schizophrenia development through family screenings and genotyping [114]. Whole-genome sequencing has also linked *ELAVl2* to autism spectrum disorders [49]. Regionally, Elavl2 exhibits cell-specific expression patterns in the hippocampus, primarily localized to CA3 pyramidal neurons and hilar interneurons. In a kainic acid (KA)-induced epilepsy model, Elavl2 protein expression was significantly reduced in CA3 neurons, along with reduced mRNA levels of the downstream factor GAP-43. These results suggest that Elavl2 is regulated by the KAKAR signalling axis and plays a role in activity-dependent RNA regulation [115]. Interestingly, Elavl2 is the only Elav protein expressed in honeybees, where alternative splicing produces over 40 protein isoforms involved in the brain's mushroom bodies, which are centres for olfactory learning and memory. These regulatory mechanisms may be further influenced by nuclear localization via microexons within the variable hinge region of *Elavl2* [116].

Beyond neurons, *Elavl2* has been found to be highly conserved and enriched in human spermatogonia and mouse gonads, where it is primarily localized in the nucleus and is essential for the proliferation and survival of spermatogonia.

Elavl2 plays a crucial role in the post-transcriptional regulation of spermatogonial stem cell maintenance and differentiation. During mouse development, *Elavl2* expression begins in testicular gonadal cells at E13.5 and remains elevated during testicular development, but decreases rapidly following spermatogonial stem cell differentiation. A similar pattern is observed in human testicular development. In vitro studies have shown that Elavl2 promotes spermatogonia proliferation and inhibits apoptosis by activating the ERK and AKT signalling pathways and increasing the expression of c-Fos and Myc proteins [117]. In female mice ovaries, Elavl2 is involved in the regulation of P-body mRNA, which is associated with RNA decay and cytoplasmic RNP granule storage. Elavl2 also promotes the assembly of P-body granules by enhancing DDX6 translation in oocytes, a process essential for primordial follicle formation [118].

The structure and function of Elavl3 protein

Elavl3 protein is highly expressed in the mature cerebral cortex and shows a unique expression pattern compared to Elavl3 and Elavl4. Specifically, Elavl3 is expressed in Purkinje cells and the hippocampus of the cerebellum, indicating its potential role in regulating cerebellar cell differentiation and maintaining cerebellar structure and function [119]. This hypothesis was confirmed using an *Elavl3* whole-body knockout model, where the deletion of *Elavl3* had no apparent effects on the overall health, vitality, or lifespan of the mice. However, Elavl3 plays a crucial role in maintaining the morphology and axonogenesis of cerebellar Purkinje cells. It regulates the polarity of Purkinje neurons by mediating specific splicing events in G protein-coupled receptors in embryonic exons. Loss of *Elavl3* leads to Purkinje cell swelling, formation of spherical cell bodies, and axonal degeneration, disrupting synaptic connections with the cerebellar nuclei, which causes severe cerebellar ataxia and progressive motor dysfunction. The absence of *Elavl3* also decreases neuronal excitability, impairing motor function. Ince-Dunn et al. utilized HITS-CLIP technology to demonstrate that Elavl3 binds to U-rich regions in glutamine synthetase mRNA, regulating the glutamate synthesis pathway and promoting normal neuronal electrical activity [120]. The proposed mechanism suggests that *Elavl3* deficiency results in impaired selective splicing of glutaminase RNA, leading to imbalances in the glutamate network, potentially increasing susceptibility to epilepsy. Indeed, haploinsufficiency or heterozygous mutations in *Elavl3* have been linked to spontaneous epilepsy. In *Elavl3* knockout mice, symptoms of epilepsy include transient clonic convulsive seizures and high-frequency neuronal electrical activity [120]. Additionally, *Elavl3* loss affects selective polyadenylation, producing different 3′UTR lengths in target genes and leading to the downregulation of neural markers Gad1 and TubβIII, which delays the differentiation of GABAergic neurons [121]. Elavl3 plays a key role in the development and functioning of nerve cells, particularly in the formation and maintenance of glutamatergic excitatory neurons. Studying the role of Elavl3 offers new insights into the pathogenesis and potential treatments for neuronal axonal degeneration.

The structure and function of Elavl4 protein

The gene encoding *Elavl4* is located on chromosome 1p34 in humans and 49.5 cM on chromosome 4 in mice. The mouse *Elavl4* gene spans approximately 146 kb and contains seven exons (exon 2 to exon 8) that span about 44 kb of DNA [122]. Among nElavls, Elavl4 was the first member to be discovered and successfully replicated, and it remains the most extensively studied. Studies have shown that *Elavl4* mRNA can be detected as early as E10.5 in the embryonic brains of mice and rats, peaking at E16.5 and gradually decreasing postnatally [123]. Elavl4 binds to around 1304 mRNAs, including those encoding mTORC1-responsive ribosomal proteins and translation factors. Our previous research demonstrated that Elavl4 binds to Satb1 to regulate Neurod1, promoting the differentiation of retinal progenitors and amacrine cells [109]. Beyond its role in neuronal proliferation and differentiation, Elavl4 also influences neurite growth. Mutations in the *Elavl4* gene during early embryonic development lead to transient abnormalities in the hypoglossal and glossopharyngeal nerves, as well as reduced neural progenitor proliferation. In *Elavl4*-deficient mice, abnormal hindlimb reflexes are observed, though no significant neurodegeneration occurs [124]. In the adult brain's subventricular zone (SVZ), Elavl4 stabilizes the mRNA of adenine-thymidine (AT)-rich SATB1, promoting the differentiation of neural stem/progenitor cells into neurons. Knockout mice lacking *Elavl4* exhibit an increase in neural progenitor cells but reduced early neuronal differentiation, suggesting that Elavl4 regulates multiple stages of neurodevelopment [125]. Specifically, Elavl4 appears to negatively regulate neural progenitor cell proliferation [24], facilitating the exit of neuronal precursor cells from the cell cycle and promoting the differentiation of postmitotic neurons [126]. While much of the research on Elavl4 focuses on its role in neurogenesis, it also plays an essential part in neuronal function, survival, learning, memory, and synaptic plasticity after injury [120,127]. In developing neurons, Elavl4 is localized in axon growth cones, and in mature neurons, it is found in axons and dendrites, where it promotes neurite growth. The protein regulates the stability and expression of target mRNA products, including brain-derived neurotrophic factor (BDNF), GAP-43, Tau, acetylcholinesterase (AChE), c-Fos, and N-myc [128,129]. Elavl4 promotes axonal formation, microtubule assembly, and growth cone development, playing a neuroprotective role by enhancing axonal growth and contributing to synaptic plasticity mechanisms [130]. In the dorsal root ganglion (DRG), Elavl4 promotes axonal regeneration after injury. Silencing *Elavl4* leads to decreased axonal regeneration, and its loss disrupts dendrite formation in pyramidal neurons and reduces motor neuron axons [131]. These findings indicate that Elavl4 plays a critical role in the dendrite formation of specific neuronal subtypes.

Elavl4 is also expressed in glutamatergic neurons in the hippocampus and neocortex, where it regulates neuronal excitability in neural circuits. It has been implicated in neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD), as well as motor neuron diseases such as spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS). Multiple studies have shown that

genetic variations in ELAVL4 are closely linked to the age at onset of Parkinson's disease (PD). Replication studies, such as GenePD, have confirmed these associations [132], and additional research has localized ELAVL4 to the PARK10 locus – suggesting that its variability may influence PD risk [133]. Notably, kinases like LRRK2 (commonly mutated in familial PD) can phosphorylate HuD, a modification that may alter its RNA-binding properties and indirectly lead to abnormal expression of multiple downstream genes, thereby contributing to PD pathology [47,103]. Moreover, changes in HuD expression disrupt the mRNA networks essential for maintaining synaptic structure and function, accelerating the degeneration of midbrain dopaminergic neurons and further driving PD progression [47]. Additionally, Elavl4 binds to the long non-coding RNA BACE1-AS, stabilizing it and further enhancing *BACE*1 production, thus contributing to Aβ formation [134]. In motor neurons, Elavl4 interacts with survival motor neuron (SMN) protein, influencing target mRNA levels and axon and dendrite development. A deficiency in *Elavl4* or reduced SMN protein levels can result in defects in motor neuron development and synapse formation, leading to spinal muscular atrophy [135]. Moreover, Elavl4 stabilizes the long 3′UTR variant of *SOD*1 mRNA, suggesting that it contributes to the pathogenesis of ALS through post-transcriptional regulation of *SOD*1 and by influencing oxidative stress. Thus, Elavl4 May represent a novel biomarker or therapeutic target for treating ALS [127]. In summary, Elavl4 binds to target mRNAs to promote neuronal maturation and function, and it may contribute to neurodegenerative diseases through its regulation of mRNA stability.

Summary and prospect

The RNA-binding protein ELAV/Hu family, which includes four key members (Elavl1, Elavl2, Elavl3, and Elavl4), plays critical roles in post-transcriptional gene regulation. While Elavl1 (HuR) is broadly expressed in various tissues and regulates cell proliferation, differentiation, and stress responses, its roles in organismal growth, ageing, tumorigenesis, and oxidative stress have been extensively characterized. In contrast, the other three members – collectively referred to as neuronal ELAVs (nELAVs) – are predominantly expressed in the nervous system, where they are essential for neuron-specific RNA regulation. Recent evidence suggests that the duplication events generating the four ELAV family members are relatively recent and consistent with the 'out of testis' hypothesis, as several of these genes exhibit high expression in reproductive tissues, implying that testis-specific factors may have driven their emergence. Future studies integrating gene age estimation tools (e.g. phylostratigraphy) and single-cell transcriptomics of human gonads may clarify whether ELAV family members represent evolutionarily young genes co-opted for reproductive functions [136].

The evolutionary conservation of ELAV/Hu proteins across species offers a unique perspective on functional evolution. In *Drosophila*, for example, ELAV/Hu proteins regulate neuronal mRNA alternative polyadenylation (APA) through overlapping activities that shape the 3′ UTR landscape critical for neurodevelopment [137]. Similarly, research in plants has shown that rice ELAV/Hu homologs (e.g. EHL1) directly bind to MADS-box transcripts to regulate floral organ development, suggesting that these proteins may have played an ancient role in developmental patterning that predates the divergence of animals and plants [138]. Future comparative studies of structural motifs, such as the RRM domains, across different kingdoms could reveal conserved regulatory principles alongside lineage-specific innovations.

Beyond neuronal maintenance, emerging evidence highlights a role for ELAV/Hu proteins in cancer biology. Elavl4 is considered a potential oncogene in glioblastoma because it stabilizes pro-survival mRNAs, while HuR (Elavl1) promotes tumour progression in hepatocellular carcinoma and gastric cancer, with its high cytoplasmic expression linked to poor prognosis [139]. Inhibitors such as CMLD-2, targeting HuR-RNA interactions, are in preclinical testing and may lead to therapies against nELAVs [140]. Moreover, there is a provocative possibility that nELAVs might be exploited to modulate tumour immunogenicity through their effects on the stability of immune checkpoint gene transcripts. In addition to their established roles in neuronal processes, ELAV/Hu proteins display remarkable versatility. In humans, nELAVs have been detected in germ cells where they may help safeguard meiosis-specific transcripts, indicating a broader functional spectrum than previously thought. Systemic dysregulation of HuR in metabolic diseases such as non-alcoholic steatohepatitis further hints at potential cross-talk between RNA-binding proteins and metabolic signalling – a frontier that remains to be fully explored.

Looking towards the future, several promising research directions emerge. Synthetic biology applications, such as engineering nELAVs with programmable RNA-binding domains (e.g. CRISPR-Cas13 fusion proteins), could allow for precise control of transcript stability in gene therapy. Advancements in dynamic RNA imaging, including technologies like vLUME VR, may enable real-time visualization of nELAV-RNA interactions within three-dimensional neuronal networks. Preliminary evidence that HuR modulates circadian clock genes raises the question of whether nELAVs integrate RNA metabolism with circadian rhythms, particularly in the context of neurodegeneration. Furthermore, exploring plant – animal hybrid systems – using rice EHL1 mutants to determine if animal ELAV proteins can rescue developmental defects – could provide valuable insights into the evolutionary conservation and divergence of these regulatory proteins.

In summary, the Elav/Hu family exemplifies how RNA-binding proteins bridge molecular specificity with systemic adaptability. While current research has illuminated their crucial roles in neurodevelopment and cancer, emerging tools – from spatial omics to RNA-targeted therapeutics – promise to unravel their complete mechanistic spectrum. By embracing cross-disciplinary approaches in evolutionary biology, synthetic immunology, and beyond, future studies could transform these proteins from mere molecular players into foundational pillars of precision medicine.

Disclosure statement

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Author contribution statement

Y.S. designed the project. H.W. drafted the manuscript. W.X. and X. T. assisted in data collection and study design. All authors read and approved the final manuscript.

Data availability statement

I confirm I understand the terms of the share upon reasonable request data policy.

I confirm I have included a Data Availability Statement in my manuscript

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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