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Role of HuD in nervous system function and pathology

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1. ABSTRACT

Hu proteins are a family of RNA-binding proteins (RBPs) that are homologs of *Drosophila* ELAV, a protein required for nervous system development. Three of these proteins (HuB, HuC, and HuD) are primarily expressed in neurons. The fourth member, HuR is ubiquitously expressed in all tissues. At the molecular level, Hu proteins are known to interact with AU-rich instability conferring sequences in the 3' UTR of specific target mRNAs, stabilizing the mRNAs. These proteins are not only the best known mRNA stabilizers but also the earliest markers of the neuronal cell lineage. Among the neuronal Hu proteins, HuD has been shown to accelerate neuronal differentiation and axonal outgrowth in neurons both in culture and *in vivo*. In addition, HuD and other Hu proteins participate in synaptic plasticity mechanisms in the mature central nervous system and promote regeneration of peripheral nerves. Furthermore, HuD has been implicated in pathological conditions from neurodegenerative disorders such as Parkinson's and Alzheimer's disease to childhood brain tumors. This review will focus on the involvement of HuD in nervous system function and pathology.

2. INTRODUCTION

Hu proteins are a family of RNA-binding proteins that were first detected as the targets of autoantibodies found in patients with paraneoplastic encephalomyelitis (1). These proteins are homologs of ELAV (embryonic lethal abnormal vision), a *Drosophila* RNA-binding protein identified because of the lethality shown by its deletion (2). Although there is only one ELAV protein in *Drosophila*, four mammalian ELAV-like Hu proteins have been identified [HuR, HuB (a.k.a.Hel-N1), HuC and HuD]. Three of these proteins (HuB, HuC, and HuD) are expressed in neurons while the fourth member, HuR, is ubiquitously-expressed in all tissues. At the molecular level, all four ELAV-like Hu proteins contain three RNA recognition motifs (RRMs), a highly conserved 80 amino acid region that was first recognized in splicing factors and poly(A)-binding protein (3, 4). The RRMs are highly conserved among members of the family while the amino terminus and a basic domain between RRMs 2 and 3 are very diverse. RRMs 1 and 2 in Hu proteins bind AU-rich elements (ARE) found in the 3'UTRs of several unstable mRNAs involved in cell growth and differentiation (5, 6). In contrast, the third RRM is

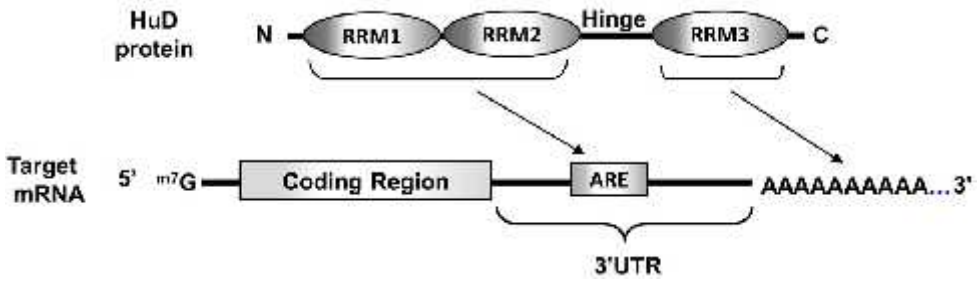

Figure 1. Diagram of the interaction of the RNA-binding protein HuD with its target mRNAs. The RNA-Recognition motifs (RRMs) 1 and 2 in HuD are known to interact with AU-rich elements (AREs) in the 3' UTR of targets mRNAs while RRM3 is known to bind long poly(A) tails. See text for details.

important for the interaction of the protein with long poly (A) tails (7, 8) (Figure 1). Recent studies indicate that Hu proteins are involved in various aspects of mRNA regulation, from mRNA processing and stability to translation (9-13).

3. Hu PROTEIN FUNCTION IN NEURONS

3.1. Role of Hu proteins in neuronal development

In *Drosophila*, deletion of the *elav* gene is embryonic lethal due to the failure of neurons to differentiate (2, 14). The continued expression of ELAV in adult neurons is essential for brain function, as temperature-sensitive mutants become incapacitated at non-permissive temperatures (15). In higher vertebrates and mammals, Hu proteins are one of the earliest markers expressed in neurons (16). HuR is the first protein to be expressed in chicken embryos where it is thought to be involved in cell proliferation (17). HuR is mainly nuclear and shuttles to the cytosol (18, 19) while HuD and other Hu proteins are localized to the cytoplasm (20-22). The expression of HuD coincides with the earliest stages of neuronal differentiation and is maintained through the maturation of neurons (17). Similar types of expression patterns have been observed in the developing mouse (23) and rat (24, 25) brains. The involvement of Hu proteins in different stages of neuronal differentiation was confirmed by overexpression and knockout studies. Overexpression of HuB, HuC or HuD in PC12 cells and *in vivo* was shown to increase the rate of neuronal differentiation (22, 26-29). Down-regulation of these proteins in neural cell lines results in the opposite phenotype, with cells failing to grow neurites (29, 30). Neuronal Hu proteins also have a role in neural stem cell differentiation as seen by the phenotype of HuD KO mice, which show increased proliferation of stem cells in the subventricular zone but decreased production of mature neurons (31). Altogether, these findings support the notion that Hu proteins play a critical role in nervous system development.

3.2. Role of Hu proteins in synaptic plasticity

Although Hu proteins were initially described as early markers of development, in certain mature neurons significant levels of Hu proteins persist throughout life, particularly in the cortex and hippocampus. As shown in Bolognani *et al.*, 2004, (ref. 20) HuD is present in the soma and dendrites of pyramidal cells in the hippocampus and neocortex in close association with polysomes. In contrast this protein is not detected in mature dentate granule cells. The spatial pattern of expression of HuB is similar to that of HuD but distinct from HuC, which is normally expressed at high levels in dentate granule cells (23). The function of these proteins in mature neurons is not completely understood but several lines of evidence indicate that they are involved in synaptic plasticity mechanisms. First, HuD protein levels are increased in the hippocampus after different learning and memory tasks (20, 32, 33). Second, antisense-mediated knock down of HuC in the hippocampus impairs learning in the radial maze task in mice (33). Third, overexpression of HuD in transgenic mice leads to profound deficits in the performance of two associative learning and memory tests, fear conditioning and the Morris water maze (34). Finally, recent analysis of the HuD targets in the mature brain (35) revealed that several of these mRNAs are associated with long-term potentiation, a phenomenon thought to underlie learning and memory (Figure 2).

3.3. Role of HuD in nerve regeneration

In addition to participating in synaptic changes in adult neurons in the central nervous system, HuD has been implicated in the response of peripheral neurons to injury. Following sciatic nerve crush, HuD protein and transcript levels increase in dorsal root ganglia sensory neurons within 7 days and remain elevated for up to three weeks (36). This increase in HuD expression is accompanied by a dramatic increase in GAP-43 mRNA levels, a known HuD target that encodes for a growth-associated protein involved in axonal outgrowth. In regenerating dorsal root ganglion neurons, HuD protein co-localizes with GAP-43 transcripts and ribosomal proteins in cytoplasmic granules (36), suggesting that HuD contributes to stabilize GAP-43 mRNA before translation. Another study also demonstrated the co-localization of HuD and GAP-43 mRNA in ribosome containing granules in axons and growth cones (37), the sites of localized GAP-43 protein synthesis (Moon, Twiss and Perrone-Bizzozero, unpublished results). The role of HuD in nerve regeneration was further investigated using a viral vector to express exogenous human HuD in rat superior cervical ganglion neurons following axotomy (38). HuD overexpression prevented the acute downregulation of acetylcholinesterase (AChE) and GAP-43 mRNAs, leading to faster response to the injury. Together, these findings demonstrate that in addition to its

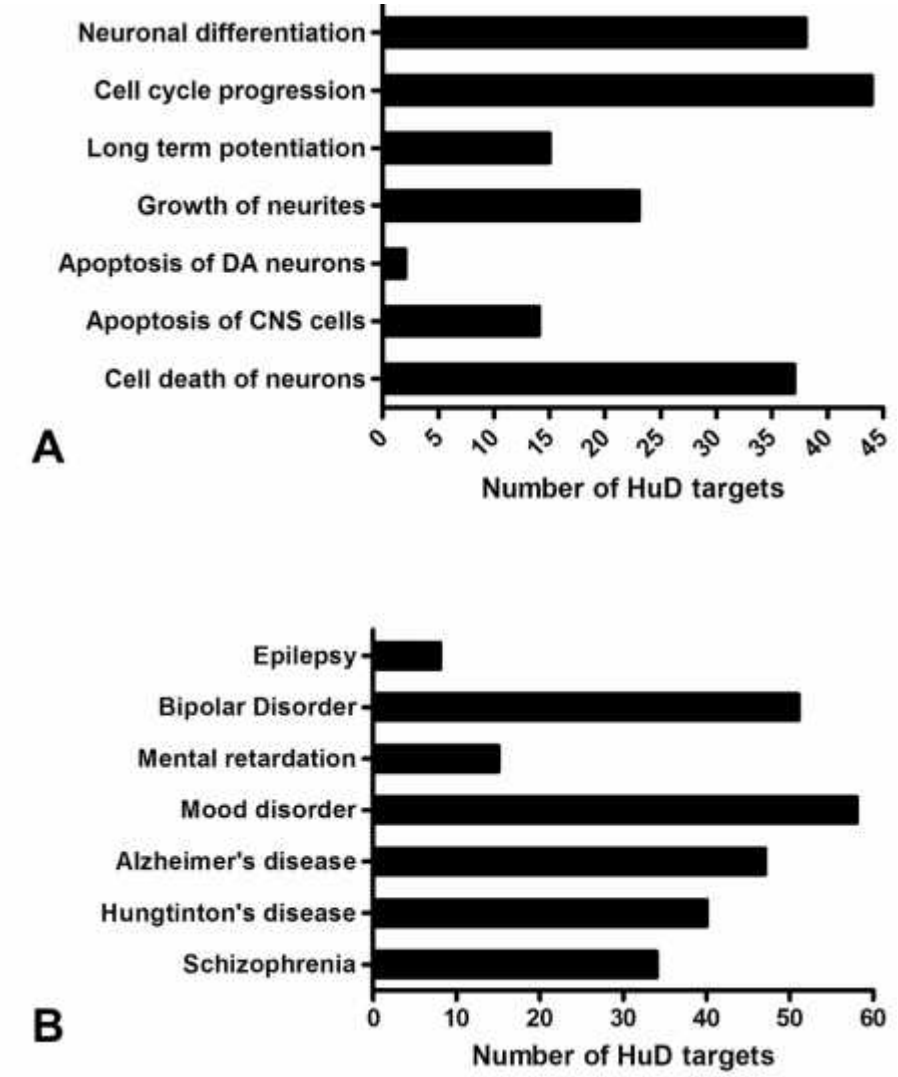

Figure 2. Association of HuD targets with nervous system function and neurological diseases. The list of HuD targets identified by Bolognani et al, 2010 (ref. 35) was uploaded onto Ingenuity Pathway Analysis (IPA). Panel A. Top functional nervous system categories significantly enriched with HuD targets. B. Neurological and psychiatric disease categories with significant HuD target enrichment.

role in neuronal development and plasticity HuD is important for the increased expression of growth-associated genes during nerve regeneration.

4. CONTROL OF HuD FUNCTION AND ITS TARGET mRNAs

4.1. Transcriptional, post-transcriptional and post-translational control

Analysis of the structure of the four genes encoding each of the Hu proteins demonstrated that these proteins not only have a high degree of sequence conservation but also that their genes have a similar genomic organization (39-41, for review see ref. 10). Although the transcriptional control of Hu protein expression has not been fully characterized, elements in the promoter regions of HuD, HuB and HuC were shown to control neuron-specific expression of these proteins (41-45). In addition, HuD transcription is known to be repressed by thyroid hormone (46), suggesting a potential dysregulation in both hypo- and hyperthyroidism. Hu proteins are also subjected to alternative splicing between RRMs 2 and 3. In the case of HuD, three alternatively-spliced isoforms have been identified: HuDpro (with exons 6 and 7 inclusion), HuD (with exon 6 inclusion) and HuDmex (excluding both exons 6 and 7). Among these isoforms, HuD is the most abundant protein in neurons followed by HuDpro. Interestingly, it was found that although Hu proteins block inclusion of specific exons in the mRNA encoding neurofibromatosis 1 (NF1) and calcitonin gene-related peptide (CGRP) (12), they promote inclusion of exon 6 in HuD (47), explaining the increased abundance of this isoform in neurons.

Another post-transcriptional mechanism involves the regulation of Hu protein levels by microRNAs. The effects of mir-519 and mir-125a on HuR levels have been well established (for further details see Subramanya and Gorospe, this series). Likewise, a recent study demonstrated that HuD levels are also controlled by microRNAs. As shown by Abdelmohsen *et al*, 2010 (48), miR-375 represses HuD expression by binding to a specific and highly conserved site on the 3' UTR, decreasing both neurite outgrowth in cultures of developing neurons and dendritic density in hippocampal neurons *in vivo*.

In addition to these post-transcriptional mechanisms, HuD, like HuR, is known to be post-translationally regulated by arginine methylation (49, 50) and phosphorylation (51). Protein kinase C (PKC)-dependent phosphorylation of HuD has been shown contribute to the stabilization of the GAP-43 (29, 51, 52) and NOVA1 mRNAs (53). HuD is also methylated at an arginine residue in the hinge region by the coactivator associated arginine methyltransferase (CARM1). The physiological role of CARM1 in the regulation of HuD activity was first described in PC12 cells induced to exit the cell cycle and differentiate in the presence of nerve growth factor (49). This treatment decreased CARM1 expression and lead to a concomitant increase in the binding of HuD to the $p21^{cip1/waf1}$ mRNA (49). A similar reduction in CARM1 protein levels was recently reported in motor neuron cells induced to differentiate with retinoid and neurotrophic factors, which also resulted in the increased interaction of HuD and $p21^{cip1/waf1}$ mRNA (54).

4.2. Mechanism of HuD-mediated mRNA stabilization of neuronal mRNAs

A detailed analysis of the mechanism by which HuD stabilizes GAP-43 mRNA (55) revealed the following requirements for this function. To be stabilized by HuD, mRNAs need to be: a) capped b) polyadenylated with long poly(A) tails, and c) contain an intact U-rich HuD binding motif in the 3' UTR. Also, HuD was found to decrease the rate deadenylation of GAP-43 mRNA, which is the first step in the reaction followed by a rapid and processive decay of the body of the mRNA (55). Analysis of HuD's protein structure indicated that all three RRMs are required for this function as a truncated protein including only RRMs 1 and 2 was not effective in stabilizing the mRNA or inducing neurite outgrowth (27).

Besides GAP-43 a number of neuronal mRNAs are known to be stabilized by HuD including those encoding c-fos, the microtubule-associated protein tau, neuroserpin, $p21^{cip1/waf1}$, N-myc and c-myc, VEGF, MARCKS, NOVA1, Musashi 1 and AChE (53, 56-63). Of these targets, a few were confirmed by cell culture studies, including GAP-43 neuroserpin, tau, NOVA1, AChE and N-myc (28, 29, 53, 57, 58, 63, 64) and two, GAP-43 and AChE were confirmed *in vivo*, in the brains of HuD overexpressor mice (21, 38).

4.3. HuD targets in neurological disorders

In addition to the mRNAs listed above, it is likely that HuD binds and stabilizes additional neuronal mRNAs containing instability-conferring sequences in their 3' UTRs. Using RNA immunoprecipitation and microarrays, we have recently identified about 600 mRNAs that bind HuD in the mouse brain (35) and thus, constitute new targets of this RBP. The majority of HuD-target interactions occur via the specific binding of HuD to three novel recognition motifs, which are mostly U-rich and localized to the 3' UTR (35). In agreement with the role of HuD in neural development and synaptic plasticity, a number of its targets are significantly enriched in the following nervous system functions: axon guidance and neurite outgrowth, long-term potentiation, cell cycle progression and neuronal differentiation (Figure 2A and ref. 35). Interestingly, HuD targets are also associated with apoptosis of dopaminergic neurons, which die preferentially in Parkinson's disease (PD), and neuronal cell death in general, suggesting the potential involvement of this RBP in neurodegenerative disorders. As shown in Figure 2B and Table 1, HuD target mRNAs are associated with a number of neurological disorders including neurodegenerative disorders such as Alzheimer's disease (AD), Huntington's disease and PD, mood disorders, epilepsy, schizophrenia and mental retardation conditions such as Rett syndrome. As discussed below, there is significant evidence showing the association of polymorphisms in the HuD (*ELAVL4*) gene with PD and the correlation of *ELAVL4* gene deletions with neuroblastoma malignancy.

5. ASSOCIATION OF HuD WITH NEUROPSYCHIATRIC DISORDERS

5.1. HuD and the genetics of Parkinson's disease

Research examining the genetic factors affecting the age-at-onset (AAO) of PD identified a genetic locus on chromosome 1p that seemed to be modulating how early PD affected patients (65, 66). The *ELAVL4* gene is contained within the chromosome 1p linkage region termed PARK10, leading researchers to investigate single-nucleotide polymorphisms (SNPs) within this gene that could be contributing to the AAO of PD. Of the nine single nucleotide polymorphisms (SNPs) within the *ELAVL4* gene initially genotyped in a US study (67), two, rs967582 and rs2494876, were significantly associated with AAO. While rs967582 is located in intron 2, rs2494876 is a non-synonymous SNP located in the most 3' exon (exon 8) of the HuD gene (67). Two additional studies, one in an Irish case-control cohort (68) and another one using an international sample of familial PD cases (69) replicated the association of rs967582 with the AAO of PD.

The non-synonymous SNP rs2494876 results in a substitution of a proline for a serine at amino acid 270, which is located in the hinge region between RRMs 2 and 3. This change could have a serious impact in the protein's secondary structure, which in turn could alter the binding of HuD to its target mRNAs and contribute to AAO of PD. The contribution of rs967582 is a little more tenuous, as this intronic SNP would not be affecting the coding sequence of HuD. Nevertheless, it is conceivable that rs967582 is linked to a different, yet unidentified, polymorphism in the *ELAVL4* gene that contributes to AAO.

Table 1. List of HuD targets associated with neuropsychiatric disorders

Diseases	HuD targets
Alzheimer's and Parkinson's disease	ACTB, ADAM10, AKAP5, APBB2, ARAP2, BACE1, BCL2L11, BECN1, CANX, CHRNA7, CNTNAP2, CRLS1, FGF12, GABRB2, GALNT13, GM2A, GNG4, GRM5, GSK3B, HIF1A, MAGI2, MAPK8, MAPT, MSI2, NALCN, NKAIN2, NPAS3, OPCML, PAK3, PLCB1, PRDX1, PRKCE, PTPRD, RAB14, RAB6A, REEP1, RIMS1, RPS6KB1, SCN2B, SERPINE2, SET, SLC1A1, SNCA, SCN2B SOD2, SPAST, STK24, STXBP6, VCL, WASF1, WDR37, XIAP, YWHAZ
Huntington's disease	ACAT1, ACTB, AHCYL1, ARPP19, ARPP21, ATP2A2, B2M, CAMKK2, CDH2, ELAVL2, ESRRG, FBXW7, FGF12, FOXG1, FOXN3, FOXP1, GABRB2, GJA1, MBNL2, NAP1L5, OSBPL8, OXR1, PCDH7, PDCL, PDP1, PLCB1, PPARGC1A, PPP1CB, PPP3CA, RAB6A, RERE, SCARB2, SCN2B, SLC1A1, TBR1, TPM3, TRAM1, XIAP, YWHAZ, ZNF706
Schizophrenia	ATF2, CALR, CDKN1B, CHRNA7, CLINT1, CNTNAP2, CUX2, ELAVL4, FZD3, GABBR1, GABRB2, GRM5, GSK3B, KIF2A, LYRM5, MAGI2, MARCKS, NCAM1, NPAS3, NPTN, PFN2, PIK3R1, PPP3CB, RIT2, SCN2B, SLC1A1, SOD2, SSTR4
Mood disorder	ATP2C1, AUTS2, B2M, CDH2, CELF2, CHRNA7, CNTNAP2, CUL3, CUX2, DIP2C, ESRRG, FAM107B, FAT1, FBXO9, FGF12, FOXN3, FRY, G3BP2, GABBR1, GABRB2, GMPS, GNAZ, GSK3B, HNRNPC, MARCKS, MBNL2, MSI2, NALCN, NCAM1, NKAIN2, NPAS3, PAN3, PDP1, PPP3CA, PRDX1, PRKCE, PRKCI, RBMS3, RERE, RGS17, RIT2, RNF111, SATB2, SCN2B, SLC1A1, SNCA, SOD2, SSR1, TBR1, TCF4, TGOLN2,TLE4, VAMP7, VKORC1L1, WASF1, ZBTB43, ZEB2
Bipolar disorder	ATP2C1, AUTS2, CDH2, CELF2, CHRNA7, CNTNAP2, CUL3, CUX2, DIP2C, ESRRG, FAM107B, FAT1, FBXO9, FGF12, FOXN3, FRY, G3BP2, GABRB2, GMPS, GNAZ, GSK3B, HNRNPC, MARCKS, MBNL2, MSI2, NALCN, NCAM1, NKAIN2, NPAS3, PAN3, PDP1, PPP3CA, PRDX1, PRKCE, RBMS3, RERE, RGS17, RIT2, RNF111, SATB2, SCN2B, SLC1A1, SNCA, TBR1, TCF4, TGOLN2, TLE4, VAMP7, VKORC1L1, WASF1, ZEB2
Epilepsy	FKBP1A GABBR1, GABRB2, KCNC2, MAPK10, PLCB1, SERPINE2, SLC1A1
Mental retardation	ATRX, AUTS2, CREBBP, CTNND2, CUL4B, PAK3
Rett syndrome	ARF6, AUTS2 CALR, DNAJB6, MREG, PKIG, SERPINE2, TCF4, YWHAE

HuD target mRNAs encoding proteins linked to neurological and psychiatric diseases. HuD targets were analyzed using IPA software to identify disease categories with significant enrichment of HuD targets and the target mRNAs associated with each disorder.

While the precise nature of HuD in AAO of PD is presently unclear, it is enticing to propose that this may be related to its interaction with the mRNAs for α-synuclein (SNCA) or tau (MAPT), two targets of this RBP (Table 1) that have been implicated in the genetics of PD (70).

5.2. HuD and Alzheimer's disease

HuD stabilization deficits are implicated in the development and progression of AD specifically through a lack of stabilization of the α-secretase ADAM10 (71). A hallmark of the AD is the presence of senile plaques that contain aggregated β-amyloid, which is a product of successive cleavage of the amyloid precursor protein (APP) by β and γ secretases (72). Cleavage of APP by ADAM10 produces soluble APP, which is non-pathogenic (71, 72).

ADAM10 and HuD protein levels are reduced in AD, suggesting that HuD could be regulating ADAM10 protein levels through post-transcriptional regulation (73, 74). Computational analysis of ADAM10 mRNA sequence demonstrated the presence of an ARE, which also contains the putative HuD binding site. Immunoprecipitation of mRNPs containing HuD demonstrated an enrichment of ADAM10 mRNA in these complexes, further implicating HuD in the regulation of ADAM10 gene expression (73).

Binding of HuD to target mRNAs is regulated in part by PKCα isoenzyme signaling (51), which may play a role in HuD regulation of ADAM10 levels. PKC isoenzyme levels are decreased in the post-mortem brain of AD patients, leading to the interesting possibility that a deficit of PKC signaling could be impairing the binding of HuD to its mRNA targets, including ADAM10 (71). As shown in Table 1, in addition to ADAM10, a number of AD associated protein mRNAs are HuD targets. Among these is the mRNA for the β-secretase BACE1, which is involved in the production of β-amyloid and a new target for the treatment of AD (72, 75). However HuD's effect on the levels of this mRNA is yet to be established.

5.3. HuD and schizophrenia

A DNA microarray study of mRNAs expressed in the prefrontal cortex of patients with schizophrenia (76) revealed that HuD mRNA levels are increased in this disorder. Clustering analyses of the data showed that not only was HuD increased in patients but also and, most-importantly, that GAP-43 was tightly co-regulated with this protein and so were other HuD targets such as neuroserpin and MARCKS. Considering that these mRNAs are also developmentally-regulated and that the expression of at least one of them, GAP-43, is increased in these patients (77), it is enticing to propose that the observed changes in these mRNAs could be due to their HuD-induced stabilization.

5.4. HuD levels in epilepsy and drug abuse

As shown in Table 1 and Figure 2B, a number of HuD targets are associated with epilepsy. Supporting a role of HuD in this disorder HuD mRNA levels were shown to increase in rat hippocampal dentate granule cells 24 hours following kainic acid induced seizures (78) and similar findings were reported in CA1 and CA3 region of the hippocampus after pilocarpine induced seizures (79). Furthermore, HuD expression is also affected by exposure to drugs of abuse such as cocaine, as shown by the increases in the levels of this mRNA either in the whole brain (79) or in the nucleus accumbens (Perrone-Bizzozero and Neisewander, unpublished observations) 24 hours after rats received a single sensitizing injection of cocaine.

5.5. HuD and spinal muscular ataxia

Spinal muscular ataxia (SMA) is an autosomal recessive neuromuscular disease characterized by the selective degeneration of lower motor neurons of the spinal cord. SMA is caused by deletions or loss-of-function mutations in the Survival of Motor Neuron (*SMN*) gene. SMN is a protein connecting neuronal splicing and axonal transport and a recent study demonstrated that HuD co-

localizes with this protein in axons (54). Furthermore, SMN was shown to recruit HuD and its target mRNAs into RNA granules, a process that depends on the presence of the Tudor domain in SMN. Finally, it was shown that HuD overexpression could compensate for the differentiation defects observed in SMN haploinsufficient motor neurons, suggesting that increasing HuD levels in these cells could lead to better treatments for SMA (54).

6. ASSOCIATION OF HuD WITH NEUROBLASTOMAS

6.1. HuD levels in different neuroblastoma subtypes

Neuroblastomas (NB) arise from embryonic neural crest and primarily affect young children. The proto-oncogene encoding N-myc (*MYCN*) is found to be amplified as well as overexpressed in a number of these cancers (64). A number of NB-derived cell lines have been used to understand the mechanisms of carcinogenesis. Phenotypically these lines are diverse but can be classified into two main subtypes: neuroblastic N-type cells, which are non-adherent and very tumorigenic and substrate adherent S-type cells, which are not tumorigenic. N-myc is believed to maintain the proliferative, undifferentiated state of cells during development (80). HuD expression levels are high in N-type but absence in S type cells, creating the possibility that HuD may stabilize N-myc transcripts and push the cells towards a cancerous fate (81).

In vitro experiments showed that HuD binds to elements in the 3' UTR of N-myc mRNA (81). Ectopic HuD expression in stable cell lines leads to the stabilization of a reporter gene expressing the N-myc 3'UTR (64). Conversely, treatment of cells with anti-sense oligomers against HuD lead to a decrease in N-myc reporter levels, implicating HuD as the main factor regulating the stability of this mRNA (64). In addition to stabilization of the mature N-myc transcripts, HuD-induced pre-mRNA processing and stability has been reported in these cells (82).

6.2. ELAVL4 haploinsufficiency and NB malignancy

The posttranscriptional regulation of N-myc transcripts is not the only mechanism by which HuD is involved in neuroblastoma progression. About 30% of neuroblastomas with a clinically poor prognosis contain an amplification of the *MYCN* gene and a deletion in the small arm of chromosome 1 where the *ELAVL4* gene is located (83, 84). Moreover, higher HuD expression levels in neuroblastoma cells were correlated with a better clinical outcome in patients (85). Supporting a role of HuD in decreasing malignancy, overexpression of HuD in two neuroblastoma cell lines with high *MYCN* amplification was shown to decrease both cell proliferation and *MYCN* gene copy numbers (86). In contrast, knockdown of HuD levels in non-amplified SY5Y cells had the opposite effect, causing decreased HuD levels and selecting for cells with multiple copies of the *MYCN* gene (86). Although the precise mechanism of *MYCN* amplification remains to be established, one possible explanation for these findings is that cells with HuD haploinsufficiency, which normally would have lower N-myc levels, will not survive in culture unless they contain multiple *MYCN* copies, which will give them a growth advantage over non-amplified cells (86).

7. PERSPECTIVE

Altogether the data presented above supports the idea that HuD and other neuronal Hu proteins play a critical role in the post-transcriptional control of gene expression during nervous system development and plasticity. As shown in Figure 2A, HuD targets are involved in different aspects in the life of a neuron from cell cycle progression and neuronal differentiation to proper maturation and cell death. Therefore, it is not surprising that many of these same target mRNAs are associated with various neuropsychiatric disorders, from mental retardation and schizophrenia to neurodegenerative disorders such as Parkinson's and Alzheimer's disease (Table 1 and Figure 2B). The role of HuD in Parkinson's disease is also supported by genetic linkage studies demonstrating a significant association of two polymorphisms in the *ELAVL4* gene with AAO of PD. The recent findings that deletions in the *ELAVL4* gene are associated with increased malignancy in neuroblastoma cell lines not only highlight the function of this RBP in cell cycle arrest but also suggest that gene therapy directed at increasing HuD levels in neuroblastoma cells could lead to more effective treatments of those NB patients with the worst prognosis. Likewise, it is possible that that HuD overexpression could help rescue part of the motor neuron death phenotype in patients with SMA. Finally, the changes in HuD expression in response to epileptic seizures and cocaine exposure suggest a role of HuD in these disorders. From a biomedical perspective, the elucidation of the mechanisms controlling how HuD regulates the stability and translation of its target mRNAs and how these RNA-protein interactions respond to environmental cues has potential implications for the understanding a broad range of conditions from normal development and synaptic plasticity to neurodevelopmental disorders and neurodegenerative diseases.

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Abbreviations: RBP, RNA-binding protein; ARE, AU-rich element; UTR, untranslated region; RRM, RNA recognition motif; GAP-43, growth-associated protein 43; AChE, acetylcholinesterase, PD, Parkinson's disease, AD, Alzheimer's disease; AAO, age-at-onset; SNP, single nucleotide polymorphism, NB, neuroblastoma

Key Words: RBP, RNA-binding protein, ARE, AU-rich element, UTR, Untranslated region, RRM, RNA Recognition motif, GAP-43, Growth-associated protein 43, AChE, Acetylcholinesterase, PD, Parkinson's disease, AD, Alzheimer's disease, AAO, age-at-onset, SNP, Single Nucleotide Polymorphism, NB, Neuroblastoma, Review

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