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Cholinesterase-targeting microRNAs identified *in silico* affect specific biological processes

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MicroRNAs (miRs) have emerged as important gene silencers affecting many target mRNAs. Here, we report the identification of 244 miRs that target the 3′-untranslated regions of different cholinesterase transcripts: 116 for butyrylcholinesterase (BChE), 47 for the synaptic acetylcholinesterase (AChE-S) splice variant, and 81 for the normally rare splice variant AChE-R. Of these, 11 and 6 miRs target both AChE-S and AChE-R, and AChE-R and BChE transcripts, respectively. BChE and AChE-S showed no overlapping miRs, attesting to their distinct modes of miR regulation. Generally, miRs can suppress a number of targets; thereby controlling an entire battery of functions. To evaluate the importance of the cholinesterase-targeted miRs in other specific biological processes we searched for their other experimentally validated target transcripts and analyzed the *gene ontology* enriched biological processes these transcripts are involved in. Interestingly, a number of the resulting categories are also related to cholinesterases. They include, for BChE, *response to glucocorticoid stimulus*, and for AChE, *response to wounding* and two child terms of *neuron development: regulation of axonogenesis* and *regulation of dendrite morphogenesis*. Importantly, all of the AChE-targeting miRs found to be related to these selected processes were directed against the normally rare AChE-R splice variant, with three of them, including the neurogenesis regulator miR-132, also directed against AChE-S. Our findings point at the AChE-R splice variant as particularly susceptible to miR regulation, highlight those biological functions of cholinesterases that are likely to be subject to miR post-transcriptional control, demonstrate the selectivity of miRs in regulating specific biological processes, and open new venues for targeted interference with these specific processes.

Keywords: AChE, BChE, microRNA

INTRODUCTION

MicroRNAs (miRs) are small RNA molecules which target many mRNA transcripts, leading to their post-transcriptional silencing (Bartel, 2009). Many mRNAs can be silenced by multiple miRs and miRs often target more than one mRNA participating in a particular biological function (Bartel, 2009). Together, this suggests that the miR networks affecting specific mRNA transcripts may provide useful information on the biological roles in which these transcripts are involved. Cholinesterases are involved in many biological functions (Massoulie, 2002). However, miR-132 is the only miR so far that has been experimentally validated as targeting AChE, with consequences on inflammatory responses (Shaked et al., 2009). To delineate additional miRs which might regulate cholinesterase functions, we explored the 3′-untranslated regions (3′-UTR) of human cholinesterase transcripts (acetyl- and butyrylcholinesterase, AChE, BChE; Soreq and Seidman, 2001).

Given that several of the proteins involved in a specific function are often repressed by the same miR (Girardot et al., 2010), changes in a particular miR might down-regulate the entire process. Hence, we surmised that those functions that are shared by cholinesterases and the other targets of the cholinesterase-complementary miRs would be more susceptible for being affected by miR control than other processes. That concept is schematically presented as a workflow in **Figure 1**.

MATERIALS AND METHODS

MicroRNA candidates were identified on each of the 3′-UTR sequences of AChE and BChE, which are 235, 1030, and 478 nucleotides long for BChE, the major "synaptic" AChE-S variant and the stress-inducible AChE-R variant, respectively (**Figure 2A**). We used the PicTar[1], miRanda[2], miRbase[3], and microCosm[4] algorithms to identify these transcript-specific miRs. All predictions ensured a threshold P-value < 0.05, and analysis specifications allowed both evolutionarily conserved and non-conserved miRs, which enabled us to include primate-targeting miRs as well.

Validation of miR-target interactions generally involved a 3′UTR luciferase assay. In some cases, it was complemented by protein blots, real-time RT-qPCR, microarrays, transgenic technology, β-galactosidase, or GFP-tagged targets. See, for example

[1] www.pictar.mdc-berlin.de
[2] www.microRNA.org
[3] www.mirbase.org
[4] http://www.ebi.ac.uk/enright-srv/microcosm/htdocs/targets/v5/

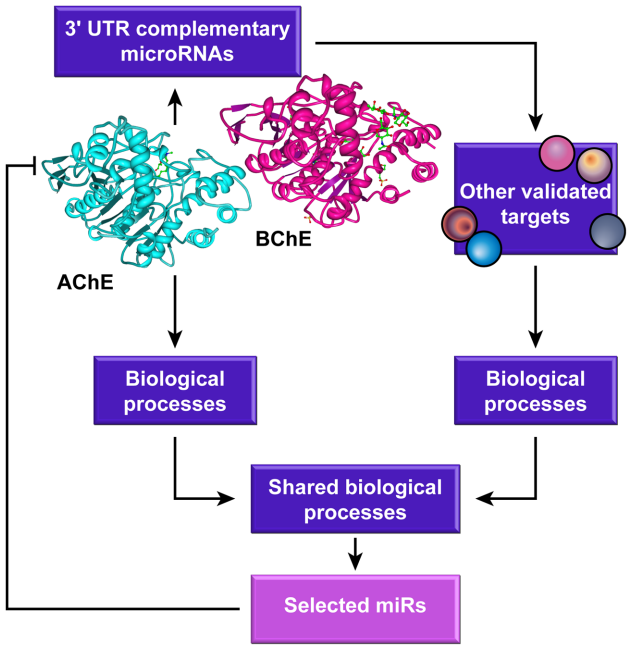

FIGURE 1 | The study's flow chart. MicroRNAs complementary to the 3′-UTR domains of AChE and BChE transcripts were identified using several algorithms and other validated targets for those miRs were searched for and analyzed for common biological processes in which both these miR targets and cholinesterases are involved.

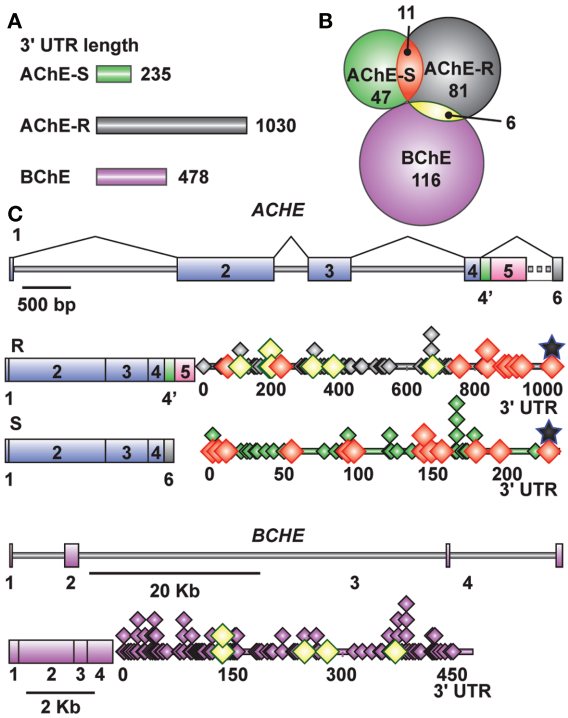

FIGURE 2 | Cholinesterase-targeted miRs show distinct 3′UTR distributions and partial overlaps. (A) The length of the studied 3′UTR domains. **(B)** Each 3′-UTR is targeted by many different miRs, part of which shared by BChE/AChE-R and AChE-R/AChE-S. **(C)** Gene and transcript compositions (exons shown as boxes, introns – as lines) and miR distribution patterns on the 3′-UTR domain (not to scale). Overlaps are color coded. MiR (diamonds) localizations are marked. Black stars show miR-132 position.

the Shaked et al. (2009) report for several of the latter technologies used to explore the miR-132 target AChE, and (Hansen et al., 2010) for the "classical" 3′-UTR and transgenic approaches, in exploring p250GAP which is also a miR-132 target.

To search for gene ontology (GO) categories which are also relevant for the other mRNA targets of cholinesterase-related miRs, we used the DAVID functional annotation clustering tool[5]. For each of the miRs identified as targeting one of the cholinesterases we searched for other experimentally validated targets; and we then used the lists of the other validated targets as gene lists for the DAVID search. Each list was normalized to the entire human genome, which served as a background.

RESULTS

We identified 116, 81, and 47 miRs (24, 8, and 20 miRs/100 nucleotides) that are complementary to the 3′-UTR domains of the BChE, AChE-R, and AChE-S transcripts, respectively. Of these, 6 miRs target both BChE and AChE-R whereas 11 miRs are common to both AChE-R and AChE-S, but BChE and AChE-S do not share any miR (**Figure 2B**). Positions of the identified miRs are presented in **Figure 2C**, with miR-132 targeting a similar seed domain localized at the very 3′-end of the 3′-UTR in both the AChE-S and AChE-R transcripts. Of the cholinesterase-targeting miRs, seven had multiple binding sites to the target AChE-S, nine to AChE-R, and seven to the BChE transcript, suggesting that they have a higher prospect for being functional (John et al., 2004).

[5]http://david.abcc.ncifcrf.gov/

Compatible with the different conceptual principles on which each of the algorithms employed is based, only 8.6, 17, and 13.7% (7/81), (8/47), (16/116) of the miRs identified as targeting AChE-R, AChE-S, and BChE, respectively, were predicted by more than one of the algorithms. For AChE-R, these are hsa-miR-28-5p, -423-3p, -484, -483-5p, -663, -582-3p, -380*. For AChE-S, hsa-miR-194, -939, -658, -608,-615-5p, -423-5p -920, and let-7f-2* and for BChE, hsa-miR-203, -218, -221, -222, -181a, -181b, -181c, -181d, -494, -200b, -200c, -576-3p, -16-2*, -625, -195*, -889.

These cholinesterase-targeting miRs and their other validated non-cholinesterase targets are listed in **Tables 1–3** with the corresponding functions attributed to these other targets. The relevant citations appear in **Tables A1–A4** in Appendix. Of note, numerous cholinesterase-targeting miRs have no experimentally validated targets at this time, yet others have more than one validated target and associate with more than one biological function. Examples include miR-124 which targets both the AChE-S and IQGAP1-(Furuta et al., 2010), a GTPase activating protein which promotes neurite outgrowth (**Table 1**). Additionally miR-152 and miR-148a, which target AChE-R, also target the calmodulin regulating kinase CaMKIIα (Liu et al., 2010; **Table 2**). Lastly, the BChE-targeting cluster of miRs-222 and -221 also target the neuronal early immediate protein c-fos (Ichimura et al., 2010; **Table 3**).

Table 1 | Additional targets of AChE-S targeting microRNAs.

miR ID	Validated targets		
hsa-miR-491-5p	Bcl-X(L; cell death)		
hsa-miR-605	Mdm2 (ubiquitination)		
hsa-miR-608	CD44 (cell–cell/cell–matrix interaction)	CDC42 (cell division)	
hsa-miR-124	Glucocorticoid receptor	LAMC1 (laminin γ1)	IQGAP1(neurite outgrowth; Furuta et al., 2010)
	NeuroD1 (neurogenic differentiation 1)	BAF53a (chromatin remodeling)	C14orf24 (chromosome 14 ORF 24)
	Mtpn (myotrophin)	PTBP1 (splicing)	CDK6 (cyclin-dependent kinase 6)
	Mapk14 (mitogen activated protein kinase 14)	PTBP2 (splicing)	SOX9 (glial cell specification)
	CDK2 (cyclin-dependent kinase 2)	C/EBPα (transcription)	Lhx2 (transcription)
	MCP1 (monocyte chemoattractant protein 1)	FOXA2 (transcription)	EfnB1(projecting axons)
	Itgb1 (integrin 1)	VIM (cytoskeleton; Furuta et al., 2010)	NR3C2 (Mineralocorticoid and glucocorticoid receptor)
	SCP1 (synaptonemal filaments)	SMYD3 (transcription; Furuta et al., 2010)	
hsa-let-7g	C-Myc (transcription)	Collagen alpha2 (COL1A2)	Bcl-xL (cell death)
hsa-miR-196a	HOX-B7 (transcription)	SPRR2C (small proline-rich protein 2C)	Annexin A1 (exocytosis)
	S100A9 (calcium-binding protein A9)	KRT5 (keratin 5)	HOXC8 (transcription)
hsa-miR-542-3p			Survivin
hsa-miR-525-5p	VPAC1 (vasoactive intestinal peptide receptor 1)		

Table 2 | Additional targets of microRNAs targeting AChE-R.

miR ID	Validated targets		
Hsa-miR-708	MPL (thrombopoietin receptor; Girardot et al., 2010)		
Hsa-miR-28-5p	MPL (thrombopoietin receptor; Girardot et al., 2010)	OTUB1 (immune system transcription; Girardot et al., 2010)	
	N4BP1 (NEDD4 binding protein 1; Girardot et al., 2010)	TEX261 (apoptosis; Girardot et al., 2010)	MAPK1 (megakaryocyte differentiation; Girardot et al., 2010)
hsa-miR-503	ANLN (actin-binding protein anillin)	ATF6 (activating transcription factor 6)	CHEK1 (cell cycle)
	EIF2C1 (argonaute1)	KIF23 (mitotic kinesin-like protein 1)	WEE1 (mitosis regulator)
	CCNE1 (cyclin E1)	CDC25A (cell cycle)	
	CCND1 (cyclin D1)	CDC14A (CDC14 cell division cycle 14 homolog A)	
hsa-miR-148a	CaMKIIα (CNS kinase; Liu et al., 2010)	MLC1 (megalencephalic leukoencephalopathy with subcortical cysts 1)	MSK1 (histone phosphorylase)
	DNMT1 (DNA methyltransferase 1)	DNMT3B (CpG island methylation)	MITF (microphthalmia-associated transcription factor)
	CCKBR (modulates anxiety and neuroleptic activity)	EPAS1 (endothelial PAS domain-containing protein 1)	HLA-G (asthma susceptibility)
	POMC (pro-opiomelanocortin)	CAND1 (ubiquitin ligase regulation)	PXR (pregnane X receptor)
hsa-miR-152	CaMKIIα (CNS kinase; Liu et al., 2010)	DNMT1 (DNA methyltransferase 1)	
hsa-miR-125b	TNFα (tumor necrosis factor α)	ERBB2 (erythroblastic leukemia viral oncogene homolog 2)	BMPR1B (bone morphogenic receptor type 1B)
	IRF4 (interferon regulatory factor 4)	ERBB3 (erythroblastic leukemia viral oncogene homolog 3)	E2F3 (cell cycle)
	Blimp1 (zinc finger protein)	TEF (thyrotroph embryonic factor)	Bcl2 modifying factor (apoptosis)
	Vdr (vitamin D receptor)	MUC1 (adhesion)	Bak1 (pro-apoptotic Bcl2 antagonist killer 1)
	CYP24A1 (cytochrome P450 family 24A)	p53 (tumor suppressor)	SMO (smoothened receptors)
	IGF2 (insulin-like growth factor 2)	Suv39h1 (histone methyltransferase)	Stat3 (Transcription factor, binds to IL-6)
	LIN28 (translational enhancer)	NMDA receptor subunit NR2A	ATM (ataxia telangiectasia mutated)

(Continued)

Table 2 | Continued

miR ID	Validated targets		
hsa-miR-125a-5p	LIN28 (translational enhancer)	T-TrkC (neurotrophic tyrosine kinase receptor 3)	HuR (cell growth)
	p53 (tumor suppressor)	KLF13 (transcription factor)	AT-rich interactive domain 3B (transcription)
	PDPN 9 (actin organization)	Bak1 (pro-apoptotic Bcl2 antagonist killer 1)	
	N-ras (oncogene)	MEK3 (phosphorylation of MAP kinase)	
hsa-miR-214	SrGAP1(neuronal migration)	Ezh2 (stem cell identity)	N-ras (oncogene)
	JNK1 (MAPK8)	PTEN (tumor suppressor)	MEK3 (phosphorylation)
hsa-miR-199a-5p	Hif-1α (Hypoxia-inducible factor 1)	IKKβ (NFκB activation)	DDR1 (discoidin domain receptor 1)
	Sirt1 (apoptosis)		
hsa-miR-31	ICAM-1 (leukocyte adhesion protein)	Fgf13 (fibroblast growth factor 13)	Dkk-1 (canonical Wnt signaling)
	DACT-3 (epigenetic regulator of Wnt)	E-selectin (inflammation)	p16Ink4a (cell cycle)
	LATS2 (tumor suppression)	PPP2R2A (signal transduction)	Krt16 (keratin 16)
	Krt17 (keratin 17)	Dlx3 (development of ventral forebrain)	E2F6 (cell cycle)
	TIAM1 (T-cell lymphoma invasion and metastasis 1)	Fzd3 (accumulation of β-catenin)	Integrin α (fibronectin)
	M-RIP (regulation of actin)	MMP16 (blood vessels matrix remodeling)	RDX (actin filaments binding to plasma membrane)
	RhoA (signal transduction)	SATB2 (upper-layer neurons initiation)	PROX1 (CNS development)
	WAVE3 (signal transmission)		
hsa-miR-185	Six1 (limb development)		
hsa-miR-193b	Estrogen receptor α Mcl-1 (myeloid cell leukemia sequence 1)	ETS-1 (oncogene) uPA (urokinase-type plasminogen activator)	CCND1 (cyclin D1)
hsa-miR-7	Alpha-synuclein (SNCA)	SFRS1 (splicing)	ERF (cell proliferation)
	LSH (lymphoid-specific helicase)	DAP (cell death-associated protein)	MRP1 (human multidrug resistance-associated protein 1)
	Associated cdc42 kinase 1	Yan (cell differentiation)	EGFR (epidermal growth factor receptor)
	CD98 (sodium transport)	Pak1 (p21-activated kinase 1)	IGF1R (insulin-like growth factor 1 receptor)
hsa-miR-483-5p	Socs-3 (cytokine signaling)	BBC3/PUMA (apoptosis)	
hsa-miR-663	TGFβ1 (proliferation)	JunB (jun B proto-oncogene)	JunD (jun D proto-oncogene)
hsa-miR-765	TRK3 (neurotrophic tyrosine kinase)		
hsa-miR-146b-3p	IRAK1 (IL1 receptor-associated kinase 1)	EGFR (epidermal growth factor receptor)	MMP16 (degrades extracellular matrix)

Table 3 | Additional targets of BChE-targeting microRNAs.

miR ID	Validated target		
hsa-miR-203	SOCS-3 (cytokine signaling)	Lef1 (lymphoid enhancer-binding factor)	p63 (transcription)
	ABL1 (cell growth)	Barx1 (transcription)	CKAP2 (cytoskeleton associated protein 2)
	LASP1 (cytoskeletal activities)	BIRC5 (regulator of mitosis)	WASF1 (signal transmission)
	ASAP1 (membrane trafficking)	RUNX2 (runt-related transcription factor 2)	
hsa-miR-340	MITF (microphthalmia-associated transcription factor)		
hsa-miR-218	IKK-β (NFκB activation)	ROBO1 (roundabout, axon guidance receptor, homolog 1)	BIRC5 (mitosis)
	GJA1 (gap junction protein, α1)	ROBO2 (roundabout, axon guidance receptor homolog 2)	GLCE (glucuronic acid epimerase)
	PXN (paxillin, cytoskeletal protein)		

(Continued)

Table 3 | Continued

miR ID	Validated target		
hsa-miR-221	ERα (estrogen receptor α)	ICAM-1(leukocyte adhesion protein)	p27 (cell cycle)
	p57 (cyclin-dependent kinase inhibitor 1C)	DNA damage-inducible transcript 4 (DDIT4)	TIMP3 (TIMP metallopeptidase inhibitor 3)
	PTEN (tumor suppressor)	PUMA (apoptosis)	C-fos (cell proliferation; Ichimura et al., 2010)
	Bmf (apoptosis)	Mdm2 (ubiquitination)	CDKN1B (cyclin-dependent kinase inhibitor 1B)
hsa-miR-222	ERα (estrogen receptor α)	p27 (cell cycle)	PTEN (tumor suppressor)
	STAT5A (transcription)	p57 (cyclin-dependent kinase inhibitor 1C)	TIMP3 (TIMP metallopeptidase inhibitor 3)
	Bim (apoptosis)	ETS-1 (transcription)	PUMA (apoptosis)
	PPP2R2A (protein phosphatase 2A subunit B)	C-fos (cell proliferation; Ichimura et al., 2010)	ICAM-1(leukocyte adhesion protein)
	MMP1 (cleaves collagens)	SOD2 (superoxide dismutase 2)	
hsa-miR-181a	SIRT1 (apoptosis)	Ataxia telangiectasia mutated (ATM; cell cycle)	Hox-A11 (transcription)
	p27(cell cycle)	PLAG1 (transcription)	BCL2 (B-cell CLL/lymphoma 2; apoptosis)
	Bim (apoptosis)	Tcl1 (cell proliferation)	OPN (osteopontin)
hsa-miR-181b	AID (RNA-editing)	PLAG1 (transcription)	BCL2 (B-cell CLL/lymphoma 2; apoptosis)
	TIMP3 (TIMP metallopeptidase inhibitor 3)	Ataxia telangiectasia mutated (ATM; cell cycle)	SIRT1 (apoptosis)
	ZNF37A (transcriptional regulation)	ZNF83 (transcriptional regulation)	ZNF182 (transcriptional regulation)
	Mcl-1 (myeloid cell leukemia-1; apoptosis)		
hsa-miR-181c	IL2 (immune response)	BCL2 (B-cell CLL/lymphoma 2; apoptosis)	NOTCH4 (transcriptional activator)
	KRAS (GTPase activity)		
hsa-miR-181d	BCL2 (B-cell CLL/lymphoma 2; apoptosis)		
hsa-miR-494	CaMKIIδ (CNS kinase)	ROCK-1 (apoptosis)	LIF [leukemia inhibitory factor (cholinergic differentiation factor)]
	PTEN (phosphatase and tensin homolog)	TEL-AML1 (hematopoiesis)	FGFR2 (fibroblast growth factor receptor 2)
hsa-miR-129-5p	CAMTA1 (calmodulin binding transcription activator 1)	EIF2C3 (eukaryotic translation initiation factor 2C, 3)	GALNT1 (oligosaccharide biosynthesis)
	SOX4 (transcriptional activator)		
hsa-miR-30d	Galphai2 (G protein, α inhibiting activity polypeptide 2)		
hsa-miR-30c	Runx1 (runt-related transcription factor 1)	CTGF (connective tissue growth factor)	
hsa-miR-30a	SOD2 (superoxide dismutase 2)	BDNF (brain-derived neurotrophic factor)	Beclin 1 (autophagy)
	Xlim1/Lhx1 (transcription factor)		
hsa-miR-30e	Ubc9 (ubiquitin-conjugating enzyme E2I)	B-Myb (transcription factor)	
hsa-miR-320a	(Hsp20 heat-shock protein 20)	AQP1 (aquaporin 1)	AQP4 (aquaporin 4)
	TfR-1; CD71 (development of erythrocytes and the nervous system)	Mcl-1 (myeloid cell leukemia sequence 1; apoptosis)	
hsa-miR-140-5p	Smad3 (transcription)	HDAC4 (histone deacetylase 4)	
hsa-miR-519c-3p	HIF-1α (hypoxia-inducible factor 1α)	ABCG2 (exclusion of xenobiotics from the brain)	
hsa-miR-489	PTPN11 (signal transduction)		
hsa-miR-584	NXA1 (exocytosis)	ROCK-1 (actin assembly)	

We focused our survey on those functions of those miRs for which experimental validation is available. **Table 4** presents these miRs which are shared for AChE-R and AChE-S or AChE-R and BChE and some of their additional targets, highlighting the multitude of miR targets with predicted regulatory functions (e.g., the chromatin modulator zinc finger proteins ZEB1 and ZEB2 targeted by miR-200b, miR-200c, and miR-429 that are also directed to both AChE-R and AChE-S; Gregory et al., 2008). Likewise, the AChE-S-targeted miR-132 (Shaked et al., 2009; Soreq and Wolf, 2011) also targets the GTPase regulator p250GAP

Table 4 | Additional targets of ChE-targeting miRs (common to more than one ChE).

miR ID	Validated target common to ACHE-R and AChE-S		
hsa-miR-186	Pro-apoptotic P2 × 7 purinergic receptor	AKAP12 (tumor suppressor)	
hsa-miR-199b-5p	Dyrk1a (brain development)	HES1 (transcriptional repressor)	SET (apoptosis)
hsa-miR-429	ZEB1 (transcriptional repression of IL2; Gregory et al., 2008) RERE (apoptosis)	ZEB2 (SIP1; zinc finger protein; Gregory et al., 2008)	PLCgamma1(apoptosis)
hsa-miR-200b	ZEB1 (transcriptional repression of IL2; Gregory et al., 2008)	ZEB2 (SIP1; zinc finger protein; Gregory et al., 2008)	PLCgamma1(apoptosis)
	Serca2 (sarco/endoplasmic reticulum Ca2+ ATPase)	Suz12 (chromatin silencing)	Ets-1 (transcriptions factor)
	OREBP (osmotic response element)	Cyclin D1	
hsa-miR-200c	ZEB1 (transcriptional repression of IL2; Gregory et al., 2008)	ZEB2 (SIP1; zinc finger protein; Gregory et al., 2008)	PLCgamma1(apoptosis)
	VEGF (angiogenesis)	TUBB3 (neurogenesis and axon guidance)	TRPS1 (transcription factor)
	KLF13 (transcription factor)	MBNL2 (muscleblind-like protein 2)	FAP1 (apoptosis)
miR ID	**Validated targets common to ACHE-R and BChE**		
hsa-miR-24	SOD1 (superoxide dismutase 1)	ALK4 (transducer of activin)	Notch1 (Bergmann glia differentiation)
	MKK4 (survival signal in T cells)	E2F2 (cell cycle)	H2AX (histone-formation)
	FAF1 (apoptosis)	HNF4α (cell proliferation)	FURIN (processing of TGFβ1)
	DHFR (dihydrofolate reductase)	DND1(miRNA-mediated gene suppression)	
hsa-miR-212	MeCP2 (interaction with histone deacetylase) PED (apoptosis)	MYC (transcription)	Rb1(tumor suppressor)
hsa-miR-132	AChE-S (Shaked et al., 2009)	P250GAP (neuron-associated GTPase; Vo et al., 2005)	Per1 (circadian clock)
	SirT1 (apoptosis)	MeCP2 (modification of eukaryotic genomes)	p300 (chromatin remodeling)
	Jarid1a (histone demethylase) p120RasGAP (angiogenesis)	Btg2 (cell cycle)	Paip2a (translation regulation)
hsa-miR-198	Cyclin T1		
hsa-miR-194	Rac1 (GTP-binding protein) MDM2 (p53 negative regulator)	Per family (circadian)	EP300 (transcriptional co-activator)

involved in neurite extension (Vo et al., 2005; Hansen et al., 2010; **Table 4**).

The process-regulation hypothesis of miR function predicts the existence of biological functions in which both cholinesterases, and those other targets which share miRs with cholinesterases, would be involved. To challenge this hypothesis, we first identified the GO categories in which AChE and BChE are involved, and found 24 and 11 biological processes for these two proteins, respectively. Twenty-three, 13, and 18 enriched biological processes emerged as shared processes for the other validated targets of AChE-R, AChE-S, and BChE-targeting miRs, respectively (P-value threshold < 0.05).

Out of over 20 ontology categories attributed to AChE, only two are shared with the categories attributed to the other validated targets of the cholinesterase-targeting miRs. These are: *Response to wounding* (GO: 0009611; 68 transcripts) and *Neuron development* (GO: 0048666), and specifically its AChE-relevant child terms *Regulation of axonogenesis* (GO: 0050770; 78 transcripts) and *regulation of dendrite morphogenesis* (GO: 0048814; 27 transcripts). Surprisingly, all 10 miRs that regulate *Response to wounding* and *Neuron development* selectively target the normally rare, stress-responsive AChE-R transcript, (miR-186, -125b, -200c, -199a-5p, -199b-5p, -125a, -214, -7, -663, -31, and -148a) whereas only three of these miRs also target the prevalent AChE-S mRNA (miR-194, -24, and -132). For BChE, we found only one shared category out of 11 relevant ontology groups: *Response to glucocorticoid stimulus* (GO: 0051384; 119 transcripts), and no overlap with the AChE-relevant categories (**Figures 3A,B**).

DISCUSSION

Using a variety of available algorithms, we found a plethora of cholinesterase-targeted miRs. Some of these were already validated as functionally capable of silencing other mRNA transcripts. A study of the functionally relevant biological processes in which these other targets are involved revealed a highly focused overlap with only few of the biological processes in which cholinesterases participate. Given that miRs regulate targets which share biological

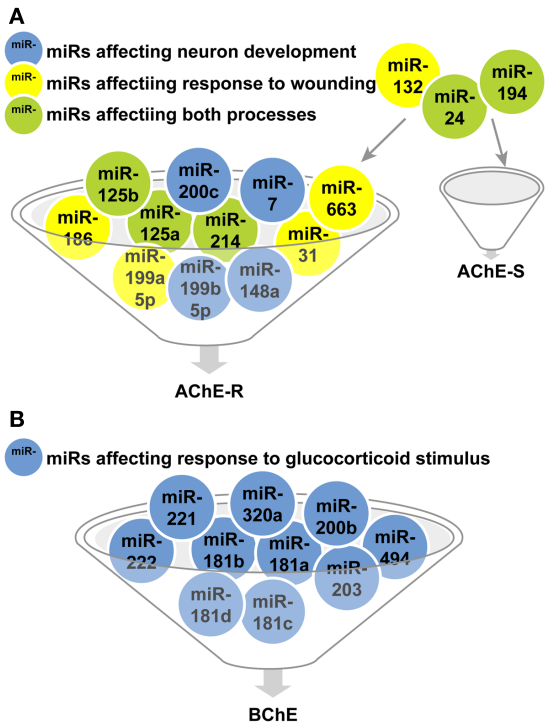

FIGURE 3 | MiR regulators of biological processes shared by cholinesterases and validated targets of these miRs. (A) miRs targeting transcripts participating in the AChE-S and AChE-R relevant *response to wounding* (yellow)and *neuron development* processes(blue) or both categories(green). **(B)** miRs targeting transcripts participating in the BChE-relevant *response to glucocorticoid stimulus* category.

processes, cholinesterases appear to be primarily subject to miR regulation when involved in neuronal development, response to wounding, and glucocorticoid stimulus; and specific cholinergic processes are regulated by miRs targeting both AChE and other targets participating in the same biological process.

Several limitations should be considered in the context of this study. First, the currently available search algorithms for miR candidates appear to differ substantially, which casts a shadow on the veracity of such identification. Second, research bias has focused much of the efforts in the miR field toward cancer research, whereas neuroscience-focused miRs were relatively neglected. Therefore, we might have overlooked important miRs simply because they have not yet been validated experimentally. This being said, that many of the biological functions in which cholinesterases are involved show no relevant cholinesterase-targeting miR sequences suggests other modes of regulation of cholinesterase levels for most of these functions [e.g., transcriptional (Hill and Treisman, 1995), epigenetic (Allshire and Karpen, 2008), or post-translational processes (Fukushima et al., 2009)]. Alternatively, or in addition, miRs might exist which control these functions, but have no role in cancer biology and are therefore not yet characterized. MiR regulation of cholinesterase functions will therefore need to be re-inspected in the near future.

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APPENDIX

Table A1 | Additional targets of AChE-S targeting microRNAs.

miR ID	Validated targets		
hsa-miR-491-5p	Bcl-X (L; cell death; Nakano et al., 2010)		
hsa-miR-605	Mdm2 (ubiquitination; Xiao et al., 2011)		
hsa-miR-608	CD44 (cell–cell/cell–matrix interaction; Jeyapalan et al., 2011)	CDC42 (cell division; Jeyapalan et al., 2011)	
hsa-miR-124	Glucocorticoid receptor (Vreugdenhil et al., 2009)	LAMC1 (laminin γ1; Cao et al., 2007)	IQGAP1(neurite outgrowth; Furuta et al., 2010)
	NeuroD1 (neurogenic differentiation 1; Liu et al., 2011)	BAF53a (chromatin remodeling; Yoo et al., 2009)	C14orf24 (chromosome 14 open reading frame 24; Ko et al., 2009)
	Mtpn (myotrophin; Krek et al., 2005)	PTBP1 (splicing; Makeyev et al., 2007)	CDK6 (cyclin-dependent kinase 6; Pierson et al., 2008)
	Mapk14 (mitogen activated protein kinase 14; Krek et al., 2005)	PTBP2 (splicing; Makeyev et al., 2007)	SOX9 (glial cell specification; Cheng et al., 2009)
	CDK2 (cyclin-dependent kinase 2; Nakamachi et al., 2009)	C/EBPα (transcription factor; Hackanson et al., 2008)	Lhx2 (transcription; Qiu et al., 2009)
	MCP- (1 monocyte chemoattractant protein 1; Nakamachi et al., 2009)	FOXA2 (transcription factor; Baroukh et al., 2007)	EfnB1(projecting axons; Arvanitis et al., 2010)
	Itgb1 (integrin 1; Cao et al., 2007)	VIM (cytoskeleton; Furuta et al., 2010)	NR3C2 (mineralocorticoid and glucocorticoid receptor; Sober et al., 2010)
	SCP1 (synaptonemal filaments; Cao et al., 2007)	SMYD3 (transcription; Furuta et al., 2010)	
hsa-let-7g	C-Myc (transcription factor; Lan et al., 2011)	Collagen alpha2 (COL1A2; Ji et al., 2010)	Bcl-xL (cell death; Shimizu et al., 2010)
hsa-miR-196a	HOX-B7 (transcription factor; Braig et al., 2010)	SPRR2C (small proline-rich protein 2C; Maru et al., 2009)	Annexin A1 (exocytosis; Luthra et al., 2008)
	S100A9 (calcium-binding protein A9; Maru et al., 2009)	KRT5 (keratin 5; Maru et al., 2009)	HOXC8 (transcription factor; Kim et al., 2009a)
hsa-miR-542-3p	Survivin (Yoon et al., 2010)		
hsa-miR-525-5p	VPAC1 (vasoactive intestinal peptide receptor 1; Cocco et al., 2010)		

miRs without validated targets: hsa-miR-920, -506, -27b, -541, -92a-2*, -658, -423-5p, -615-5p, -25*, -4688, -4776-3p, -668, -3613-5p, -4700-5p, -718, let-7f-2*, -455-3p, -633, -554, -524-3p, -638, -525-3p, -611, let-7e*, -4283, -4329, -4278, -4300, -3184, -149*.*

Table A2 | Additional targets of microRNAs targeting AChE-R.

miR ID	Validated targets		
hsa-miR-708	MPL (thrombopoietin receptor; Girardot et al., 2010)		
hsa-miR-28-5p	MPL (thrombopoietin receptor; Girardot et al., 2010)	OTUB1 (immune system transcription; Girardot et al., 2010)	
	N4BP1 (NEDD4 binding protein 1; Girardot et al., 2010)	TEX261 (apoptosis; Girardot et al., 2010)	MAPK1 (megakaryocyte differentiation; Girardot et al., 2010)
hsa-miR-503	ANLN (actin-binding protein anillin; Forrest et al., 2010)	ATF6 (activating transcription factor 6; Forrest et al., 2010)	CHEK1 (checkpoint mediated cell cycle arrest; Forrest et al., 2010)
	EIF2C1 (argonaute1; Forrest et al., 2010)	KIF23 (mitotic kinesin-like protein 1; Forrest et al., 2010)	WEE1 (mitosis regulator; Forrest et al., 2010)
	CCNE1 (cyclin E1; Forrest et al., 2010)	CDC25A (cell cycle progression; Forrest et al., 2010)	
	CCND1 (cyclin D1; Forrest et al., 2010)	CDC14A (CDC14 cell division cycle 14 homolog A; Forrest et al., 2010)	
hsa-miR-148a	CaMKIIα (CNS kinase; Liu et al., 2010e)	MLC1 (megalencephalic leukoencephalopathy with subcortical cysts 1; Geisler et al., 2011)	MSK1 (histone phosphorylase; Fujita et al., 2010)
	DNMT1 (DNA methyltransferase 1; Pan et al., 2010)	DNMT3B (CpG island methylation; Duursma et al., 2008)	MITF (microphthalmia-associated transcription factor; Haflidadottir et al., 2010)
	CCKBR (modulates anxiety, analgesia, arousal, and neuroleptic activity; Muinos-Gimeno et al., 2011)	EPAS1 (endothelial PAS domain-containing protein 1; Giraud-Triboult et al., 2011)	HLA-G (asthma susceptibility; Tan et al., 2007)
	POMC (pro-opiomelanocortin; Muinos-Gimeno et al., 2011)	CAND1 (ubiquitin ligase regulation; Murata et al., 2010)	PXR (pregnane X receptor; Takagi et al., 2008)
hsa-miR-152	CaMKIIα (CNS kinase; Liu et al., 2010e)	DNMT1 (DNA methyltransferase 1; Braconi et al., 2010a)	
hsa-miR-125b	TNFα (tumor necrosis factor α; Tili et al., 2007)	ERBB2 (erythroblastic leukemia viral oncogene homolog 2; Scott et al., 2007)	BMPR1B (bone morphogenic receptor type 1B; Saetrom et al., 2009)
	IRF4 (interferon regulatory factor 4; Malumbres et al., 2009)	ERBB3 erythroblastic leukemia viral oncogene homolog 3; Scott et al., 2007)	E2F3 (cell cycle control; Huang et al., 2011a)
	Blimp1 (zinc finger protein; Zhang et al., 2011b)	TEF (thyrotroph embryonic factor; Gutierrez et al., 2011)	Bcl2 modifying factor (apoptosis; Xia et al., 2009b)
	Vdr (vitamin D receptor; Zhang et al., 2011b)	MUC1 (adhesion; Rajabi et al., 2010)	Bak1 (pro-apoptotic Bcl2 antagonist killer 1; Zhou et al., 2010)
	CYP24A1 (cytochrome P450, family 24A, polypeptide 1; Komagata et al., 2009)	p53 (tumor suppressor; Le et al., 2009)	SMO (smoothened receptors; Ferretti et al., 2008)
	IGF2 (insulin-like growth factor 2; Ge et al., 2011)	Suv39h1 (histone methyltransferase; Villeneuve et al., 2010)	Stat3 (transcription factor binds to IL-6; Surdziel et al., 2011)
	LIN28 (translational enhancer; Zhong et al., 2010)	NMDA receptor subunit NR2A (Edbauer et al., 2010)	ATM (ataxia telangiectasia mutated; Smirnov and Cheung, 2008)
hsa-miR-125a-5p	LIN28 (translational enhancer; Wu and Belasco, 2005)	T-TrkC (neurotrophic tyrosine kinase receptor 3; Ferretti et al., 2009)	HuR (cell growth; Guo et al., 2009)
	p53 (tumor suppressor; Zhang et al., 2009)	KLF13 (transcription factor; Zhao et al., 2010)	AT-rich interactive domain 3B (transcription factor; Cowden Dahl et al., 2009)
	PDPN 9 (actin organization; Cortez et al., 2010)	Bak1 (pro-apoptotic Bcl2 antagonist killer 1; Guo et al., 2010)	
	N-ras (oncogene; Juan et al., 2009)	MEK3 (phosphorylation of MAP kinase; Li et al., 2011)	

(Continued)

Table A2 | Continued

miR ID	Validated targets		
hsa-miR-214	SrGAP1(neuronal migration; Zhang et al., 2011a)	Ezh2 (stem cell identity; Juan et al., 2009)	N-ras (oncogene; Liu et al., 2010b)
	JNK1 (MAPK8; Yang et al., 2009)	PTEN (tumor suppressor; Yang et al., 2009)	MEK3 (phosphorylation; Yang et al., 2009)
hsa-miR-199a-5p	Hif-1α (hypoxia-inducible factor 1; Rane et al., 2009)	Sirt1 (apoptosis; Rane et al., 2009)	DDR1 (discoidin domain receptor 1; Shen et al., 2010)
	IKKβ (NFκB activation; Chen et al., 2008)		
hsa-miR-31	ICAM-1 (leukocyte adhesion protein; Suarez et al., 2010)	Fgf13 (fibroblast growth factor 13; Mardaryev et al., 2010)	Dkk-1 (canonical Wnt signaling; Xi et al., 2010)
	DACT-3 (epigenetic regulator of Wnt; Xi et al., 2010)	E-selectin (inflammation; Suarez et al., 2010)	p16Ink4a (cell cycle; Malhas et al., 2010)
	LATS2 (tumor suppression; Liu et al., 2010c)	PPP2R2A (signal transduction; Liu et al., 2010c)	Krt16 (keratin 16; Mardaryev et al., 2010)
	Krt17 (keratin 17; Mardaryev et al., 2010)	Dlx3 (development of ventral forebrain; Mardaryev et al., 2010)	E2F6 (cell cycle; Bhatnagar et al., 2010)
	TIAM1 (T-cell lymphoma invasion and metastasis 1; Cottonham et al., 2010)	Fzd3 (accumulation of β-catenin; Valastyan et al., 2009)	Integrin α (fibronectin; Valastyan et al., 2009)
	M-RIP (regulation of actin; Valastyan et al., 2009)	MMP16 (blood vessels matrix remodeling; Valastyan et al., 2009)	RDX (actin filaments binding to plasma membrane; Valastyan et al., 2009)
	RhoA (signal transduction; Valastyan et al., 2009)	SATB2 (upper-layer neurons initiation; Aprelikova et al., 2010)	PROX1 (CNS development; Pedrioli et al., 2010)
	WAVE3 (signal transmission; Sossey-Alaoui et al., 2010)		
hsa-miR-185	Six1 (limb development; Imam et al., 2010)		
hsa-miR-193b	Estrogen receptor α (Leivonen et al., 2009)	ETS-1 (oncogene; Xu et al., 2010a)	CCND1 (cyclin D1; Xu et al., 2010a)
	Mcl-1 (myeloid cell leukemia sequence 1; Braconi et al., 2010b)	uPA (urokinase-type plasminogen activator; Li et al., 2009b)	
hsa-miR-7	Alpha-synuclein (SNCA; Junn et al., 2009)	SFRS1 (Wu et al., 2010b)	ERF (cell proliferation; Chou et al., 2010)
	LSH (lymphoid-specific helicase; Ilnytskyy et al., 2008)	DAP (cell death-associated protein; Yu et al., 2009)	MRP1 (human multidrug resistance-associated protein 1; Pogribny et al., 2010)
	Associated cdc42 kinase 1 (Saydam et al., 2011)	Yan (cell differentiation; Li and Carthew, 2005)	EGFR (epidermal growth factor receptor; Kefas et al., 2008)
	CD98 (sodium transport; Nguyen et al., 2010)	Pak1 (p21-activated kinase 1; Reddy et al., 2008)	IGF1R (insulin-like growth factor 1 receptor; Jiang et al., 2010)
hsa-miR-483-5p	Socs-3 (cytokine signaling; Ma et al., 2011)	BBC3/PUMA (apoptosis; Veronese et al., 2010)	
hsa-miR-663	TGFβ1 (proliferation; Tili et al., 2010b)	JunB (jun B proto-oncogene; Tili et al., 2010a)	JunD (jun D proto-oncogene; Tili et al., 2010a)
hsa-miR- 765	TRK3 (neurotrophic tyrosine kinase; Guidi et al., 2010)		
hsa-miR- 146b-3p	IRAK1 (interleukin-1 receptor-associated kinase 1; Taganov et al., 2006)	EGFR (epidermal growth factor receptor; Shao et al., 2011)	MMP16 (degrades extracellular matrix; Xia et al., 2009a)

miRs without validated targets that are predicted to target AChE-R: hsa-miR-590-3p, -148b, -193a-3p, -182, -4298, -4644, -4739, -1224-3p, -4769-5p, –582-3p, -380*, -1825, -892b, -1275, -3155, -765, -3119, -3139, -563, -92b*, -1321, -4283, -1228*, -4323, -4319, -761, -767-5p, -224*, -522, -4271, -1226*, -3179, -92a-1*, -3202, -20b*, -4303, -4306, -3065-5p, -4297, -4329, -3148, -3163, -22*, -4302, -513a-5p, -542-5p, -377*, -1908, -92a-2*, -608, -625.*

Table A3 | Additional targets of BChE-targeting microRNAs.

miR ID	Validated target		
hsa-miR-203	SOCS-3 (cytokine signaling; Wei et al., 2010)	Lef1 (lymphoid enhancer-binding factor; Thatcher et al., 2008)	p63 (transcriptional activator or repressor; Yi et al., 2008)
	ABL1 (cell growth; Bueno et al., 2008)	Barx1 (transcription factor; Kim et al., 2011)	CKAP2 (cytoskeleton associated protein 2; Viticchie et al., 2011)
	LASP1 (cytoskeletal activities; Viticchie et al., 2011)	BIRC5 (regulator of mitosis; Viticchie et al., 2011)	WASF1 (signal transmission; Viticchie et al., 2011)
	ASAP1 (membrane trafficking; Viticchie et al., 2011)	RUNX2 (runt-related transcription factor 2; Viticchie et al., 2011)	
hsa-miR-340	MITF (microphthalmia-associated transcription factor; Goswami et al., 2010)		
hsa-miR-218	IKK-β (cytokine-activated intracellular signaling pathway; Song et al., 2010)	ROBO1 (roundabout, axon guidance receptor, homolog 1; Alajez et al., 2011)	BIRC5 (regulator of mitosis; Alajez et al., 2011)
	GJA1 (gap junction protein, α1; Alajez et al., 2011)	ROBO2 (roundabout, axon guidance receptor homolog 2; Alajez et al., 2011)	GLCE (glucuronic acid epimerase; Small et al., 2010)
	PXN (paxillin, cytoskeletal protein; Wu et al., 2010a)		
hsa-miR-221	ERα (estrogen receptor α; Zhao et al., 2008)	ICAM-1 (leukocyte adhesion protein; Hu et al., 2010)	p27 (cell cycle; Garofalo et al., 2008)
	p57 (cyclin-dependent kinase inhibitor 1C; Kim et al., 2009b)	DNA damage-inducible transcript 4 (DDIT4; Pineau et al., 2010)	TIMP3 (TIMP metallopeptidase inhibitor 3; Garofalo et al., 2009)
	PTEN (tumor suppressor; Garofalo et al., 2009)	PUMA (apoptosis; Zhang et al., 2010)	C-fos (cell proliferation; Ichimura et al., 2010)
	Bmf (apoptosis; Gramantieri et al., 2009)	Mdm2 (ubiquitination; Kim et al., 2010)	CDKN1B (cyclin-dependent kinase inhibitor 1B; Kotani et al., 2009)
hsa-miR-222	ERα (estrogen receptor α; Zhao et al., 2008)	p27 (cell cycle; Garofalo et al., 2008)	PTEN (tumor suppressor; Garofalo et al., 2009)
	STAT5A (signal transducer and activator of transcription 5; Dentelli et al., 2010)	p57 (cyclin-dependent kinase inhibitor 1C; Kim et al., 2009b)	TIMP3 (TIMP metallopeptidase inhibitor 3; Garofalo et al., 2009)
	Bim (apoptosis; Terasawa et al., 2009)	ETS-1 (transcription factor; Zhu et al., 2011)	PUMA (apoptosis; Zhang et al., 2010)
	PPP2R2A (protein phosphatase 2A subunit B; Wong et al., 2010)	C-fos (cell proliferation; Ichimura et al., 2010)	ICAM-1 (Ueda et al., 2009)
	MMP1 (cleaves collagens; Liu et al., 2009)	SOD2 (superoxide dismutase 2; Liu et al., 2009)	
hsa-miR-181a	SIRT1 (apoptosis, muscle differentiation; Saunders et al., 2010)	Ataxia telangiectasia mutated (ATM; cell cycle; Wang et al., 2011)	Hox-A11 (transcription factor; Naguibneva et al., 2006)
	p27(cell cycle; Cuesta et al., 2009)	PLAG1 (transcription factor; Pallasch et al., 2009)	BCL2 (B-cell CLL/lymphoma 2; apoptosis; Zhu et al., 2010)
	Bim (apoptosis; Lwin et al., 2010)	Tcl1 (cell proliferation; Pekarsky et al., 2006)	OPN (osteopontin; Bhattacharya et al., 2010)
hsa-miR-181b	AID (activation-induced cytidine deaminase; RNA-editing; De Yebenes et al., 2008)	PLAG1 (transcription factor; Pallasch et al., 2009)	BCL2 (B-cell CLL/lymphoma 2; apoptosis; Zhu et al., 2010)
	TIMP3 (TIMP metallopeptidase inhibitor 3; Wang et al., 2010a)	Ataxia telangiectasia mutated (ATM; cell cycle; Wang et al., 2011)	SIRT1 (apoptosis, muscle differentiation; Saunders et al., 2010)
	ZNF37A (transcriptional regulation; Huang et al., 2010)	ZNF83 (transcriptional regulation; Huang et al., 2010)	ZNF182 (transcriptional regulation; Huang et al., 2010)
	Mcl-1 (myeloid cell leukemia-1; apoptosis; Zimmerman et al., 2010)		
hsa-miR-181c	IL2 (immune response; Xue et al., 2011)	BCL2 (B-cell CLL/lymphoma 2; apoptosis; Zhu et al., 2010)	NOTCH4 (transcriptional activator complex; Hashimoto et al., 2010)

(Continued)

Table A3 | Continued

miR ID	Validated target		
	KRAS (GTPase activity; Hashimoto et al., 2010)		
hsa-miR-181d	BCL2 (B-cell CLL/lymphoma 2; Zhu et al., 2010)		
hsa-miR-494	CaMKIIδ (CNS kinase; Wang et al., 2010b)	ROCK-1 (apoptosis; Wang et al., 2010b)	LIF (leukemia inhibitory factor (cholinergic differentiation factor); Wang et al., 2010b)
	PTEN (phosphatase and tensin homolog; Wang et al., 2010b)	TEL-AML1 (hematopoiesis; Diakos et al., 2010)	FGFR2 (fibroblast growth factor receptor 2; Wang et al., 2010b)
hsa-miR-129-5p	CAMTA1 (calmodulin binding transcription activator 1; Liao et al., 2008) SOX4 (transcriptional activator; Dyrskjot et al., 2009)	EIF2C3 (eukaryotic translation initiation factor 2C, 3; Liao et al., 2008)	GALNT1 (oligosaccharide biosynthesis; Dyrskjot et al., 2009)
hsa-miR-30d	Galphai2 (G protein, α inhibiting activity polypeptide 2; Yao et al., 2010)		
hsa-miR-30c	Runx1 (runt-related transcription factor 1; Ben-Ami et al., 2009)	CTGF (connective tissue growth factor; Duisters et al., 2009)	
hsa-miR-30a	SOD2 (superoxide dismutase 2; Xia et al., 2006) Xlim1/Lhx1 (transcription factor; Agrawal et al., 2009)	BDNF (brain-derived neurotrophic factor; Mellios et al., 2008)	Beclin 1 (autophagy; Zhu et al., 2009)
hsa-miR-30e	Ubc9 (ubiquitin-conjugating enzyme E2I; Wu et al., 2009)	B-Myb (transcription factor; Martinez et al., 2011)	
hsa-miR-320a	(Hsp20 heat-shock protein 20; Ren et al., 2009)	AQP1 (aquaporin 1; Sepramaniam et al., 2010)	AQP4 (aquaporin 4; Sepramaniam et al., 2010)
	The transferrin receptor 1(TfR-1; CD71; development of erythrocytes and the nervous system; Schaar et al., 2009)	Mcl-1 (myeloid cell leukemia sequence 1; apoptosis; Chen et al., 2009)	
hsa-miR-140-5p	Smad3 (transcriptional modulator; Pais et al., 2010)	HDAC4 (histone deacetylase 4; Tuddenham et al., 2006)	
hsa-miR-519c-3p	HIF-1α (hypoxia-inducible factor 1α; Cha et al., 2010)	ABCG2 (exclusion of xenobiotics from the brain; To et al., 2008)	
hsa-miR-489	PTPN11 (signal transduction; Kikkawa et al., 2010)		
hsa-miR-584	NXA1 (exocytosis; Luthra et al., 2008)	ROCK-1 (actin assembly; Ueno et al., 2011)	

miRs without validated targets: hsa-miR-147b, -532-5p, -508-3p, -889, -325, -573, -195, -567, -193b*, -625, -16-2*, -576-3p, -190b, -518e*, -518f*, -518d-5p, -147, -320d, -320c, -320b, -875-5p, -758, -30b, -1279, -3145, -1183, -664, -4261, -4262, -1237, -1972, -3146, let-7a-2*, let-7g*, -1911*, -2052, -15a*, -3148, -555, -656, -636, -3182, -513a-3p, -501-3p, -502-3p, -579, -4316, -4312, -1294, -142-5p, -3128, -30a*, -30d*, -30e*, -4268, -3137, -20b*, -651, -32*, -362-5p, -500b, -501-5p, -1976, -449c*, -1224-5p, -302a*, -1248, -99b*, -99a*, -369-3p, -1256, -629, -187*, -514b-3p, -378*, -1305, -331-5p, -1200, -4272, -4260, -493*, -582-5p, -4255, -3133, -4273, -19a*, -19b-1*, -19b-2*, -4271, -15b*, -1826.*

Table A4 | Additional targets of ChE-targeting miRs (common to more than one ChE).

miR ID	Validated target common to ACHE-R and AChE-S		
Hsa-miR-186	Pro-apoptotic P2 × 7 purinergic receptor(Zhou et al., 2008)	AKAP12 (tumor suppressor; Goeppert et al., 2010)	
Hsa-miR-199b-5p	Dyrk1a (brain development; Da Costa Martins et al., 2010)	HES1 (transcriptional repressor; Garzia et al., 2009)	SET (apoptosis; Chao et al., 2010)
Hsa-miR-429	ZEB1 (transcriptional repression of IL2; Gregory et al., 2008) RERE (apoptosis; Karres et al., 2007)	ZEB2 (SIP1; zinc finger protein; Gregory et al., 2008)	PLCgamma1(apoptosis; Uhlmann et al., 2010)
Hsa-miR-200b	ZEB1 (transcriptional repression of IL2; Gregory et al., 2008) Serca2 (sarco/endoplasmic reticulum Ca2+-ATPase; Salomonis et al., 2010) OREBP (osmotic response element; Huang et al., 2011b)	ZEB2 (SIP1; zinc finger protein; Gregory et al., 2008) Suz12 (chromatin silencing; Iliopoulos et al., 2010) Cyclin D1 (Xia et al., 2010)	PLCgamma1(apoptosis; Uhlmann et al., 2010) Ets-1 (transcriptions factor; Chan et al., 2011)
Hsa-miR-200c	ZEB1 (transcriptional repression of IL2; Gregory et al., 2008) VEGF (angiogenesis; Liu et al., 2010a) KLF13 (transcription factor; Li et al., 2009a)	ZEB2 (SIP1; zinc finger protein; Gregory et al., 2008) TUBB3 (neurogenesis and axon guidance; Cochrane et al., 2009) MBNL2 (muscleblind-like protein 2; Li et al., 2009a)	PLCgamma1(apoptosis; Uhlmann et al., 2010) TRPS1 (transcription factor; Li et al., 2009a) FAP1 (apoptosis; Schickel et al., 2010)
miR ID	**Validated targets common to ACHE-R and BChE**		
Hsa-miR-24	SOD1 (superoxide dismutase 1; Papaioannou et al., 2011) MKK4 (survival signal in T cells; Marasa et al., 2009) FAF1 (apoptosis; Qin et al., 2010) DHFR (dihydrofolate reductase; Mishra et al., 2009)	ALK4 (transducer of activin; Wang et al., 2008) E2F2 (cell cycle; Lal et al., 2009a) HNF4α (cell proliferation; Takagi et al., 2010) DND1(miRNA-mediated gene suppression; Liu et al., 2010d)	Notch1 (Bergmann glia differentiation; Fukuda et al., 2005) H2AX (histone-formation; Lal et al., 2009b) FURIN (processing of TGFβ1; Luna et al., 2011)
Hsa-miR-212	MeCP2 (interaction with histone deacetylase; Im et al., 2010) PED (apoptosis; Incoronato et al., 2010)	MYC (transcription; Xu et al., 2010b)	Rb1(tumor suppressor; Park et al., 2011)
Hsa-miR-132	AChE-S (Shaked et al., 2009) SirT1 (apoptosis; Strum et al., 2009) Jarid1a (histone demethylase; Alvarez-Saavedra et al., 2011) p120RasGAP (angiogenesis; Anand et al., 2010)	P250GAP (neuron-associated GTPase; Vo et al., 2005) MeCP2 (modification of eukaryotic genomes; Klein et al., 2007) Btg2 (cell cycle; Alvarez-Saavedra et al., 2011)	Per1 (circadian clock; Cheng et al., 2007) p300 (chromatin remodeling; Lagos et al., 2010) Paip2a (translation regulation; Alvarez-Saavedra et al., 2011)
Hsa-miR-198	Cyclin T1(Xu et al., 2010b)		
Hsa-miR-194	Rac1 (GTP-binding protein; Venugopal et al., 2010) MDM2 (p53 negative regulator; Pichiorri et al., 2010)	Per family (circadian; Nagel et al., 2009)	EP300 (transcriptional co-activator; Mees et al., 2010)

miRs without validated targets: hsa-miR-423-3p, -484, -4728-3p, -939, -484, -4728-3p.

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