

Table S2: A summary of microRNAs (miRNAs) associated with pathways related to cognitive frailty in humans

MiRNA	Function in physical/<i>cognitive</i> domains	Direction of regulation	References
miR-9 (miR-9-1, miR-9-2, and miR-9-3)	Promoter of neural progenitor proliferation CNS development; microglia activation; regulation of Lamina A transcription	Decreased in neurodegenerative traits	[125]
miR-20a	Cell proliferation and differentiation; apoptosis; APP proteolysis	Decreased in cognitive impairment	[126]
miR-21	Angiogenesis, cell differentiation and apoptosis; anti-inflammatory	Increased in human glioma cells, in SH-Y5Y cells and in LPS induced macrophages. Increased in CNS disorders	[127]
miR-23a-3p	Neuroprotection from β -amyloid toxicity	Decreased in the frontal cortex of MCI subjects	[128]
miR-26b	Synaptic maturation; Dendritic branching	Inhibition neuroprotective against oxidative stress	[129]
miR-27a-3p	Regulation of NF-kB activity, cholesterol esterification and LDL particles clearance; mitomiR	Decreased in cognitive impairment	[126]
miR-29c	Synaptic plasticity; A β clearance; dendritic branching; mitomiR	Increased levels associate with preserved cognitive function	[130]
miR-30b	Synaptic plasticity	Decreased in cognitive impairment	[131]

miR-34a/c	Synaptic transmission; A β clearance; Hypocampal function; neurotransmitter release; dendritic loss; mitomiR;	Increased in age-related inflammatory-neurodegeneration; Increased in learning and memory impairment	[132] [133]
miR92a-3p	Synaptic transmission; mitomiR	Increased in schizophrenia, altered synaptic function in MCI	[68,69]
miR-93	Angiogenesis; inflammatory response	Increased in vascular impairment	[134]
miR-103a	APP proteolysis	Decreased in cognitive impairment	[126]
miR-124	Regulation of alternative splicing in neurons; microglial polarization; inflamm-miRNA	Downregulation inhibits neuroinflammation in cellular models of neurodegeneration	[135]
miR-125b	Synaptic transmission; neurotransmitter release; tau phosphorylation	Increased levels related to neurotoxicity; Increased in MCI	[136] [137]
miR-128	Modulator of intracellular calcium content	Increased in MCI	[137]
miR-132 miR-132-3p	Regulator of cholinergic signaling; synaptic plasticity; tau aggregation; mitochondrial decline	Increased in dementia and decreased in non-demented centenarians Increased levels in MCI patients Decreased levels protect from dementia	[138] [137,139,140],
miR-134	Synaptic plasticity	Downregulation is neuroprotective in cellular models Increased levels in cognitive impairment Increased in MCI	[141] [142] [137]
miR-135	Modulator of the brain's response to physical exercise	Increased in exosome from MCI subjects	[143]

miR-137	Neuronal cell proliferation and differentiation; Pre-synaptic plasticity	Overexpression upregulated target genes related to synaptic modulation in cognitive and psychiatric disorders	[144]
miR-138-5p	Synaptic plasticity; tau phosphorylation	Overexpression associates to decreased memory performance	[145]
miR-140-5p	Negative regulator of ADAM10 and its transcription factor SOX2, activated by A β	Predictor of cognitive decline Up-regulated in dementia	[146] [147]
miR-142-3p	Regulatory T Cell Function; cell proliferation	Increased in different kind of dementia	[131]
miR-146a	Regulator of the NF- κ b pathway; tau phosphorylation; inflamm-miRNA;	Increased in neurodegenerative conditions; Overexpressed in MCI	[120] [148]
miR-155	Neuroinflammation; microglial activation; regulation of immune response; inflamm-miR; mitomiR	Increased in neurodegenerative conditions	[120]
miR-181 (miR-181a- miR-181b- miR-181c)	Synaptic plasticity; neuroinflammation; A β clearance; apoptosis; inflamm-miR; mitomiR	Overexpression in MCI patients who later convert to AD	[148]
miR-186-5p	Synaptic signalling; Amyloid-beta formation	Upregulated in AD pathogenesis	[149]
miR-193b	Regulator of APP	Increased in exosome from MCI patients	[143,150]
miR200a-3p	A β accumulation, apoptosis	Increased in different kind of dementia	[131]
miR-204	Cell migration and differentiation; microglial activation; IL6 production; prostaglandin biosynthesis	Down-regulated in hippocampal sclerosis Upregulated in serum samples from patients affected by neurodegenerative disorders	[151] [152]

miR-206	Synaptic maturation	Increased levels in MCI patients	[139]
miR-210	Vesicular trafficking; synaptic plasticity; Inflamm-miR;	Decreased levels correlate with increase in MCI severity	[153]
miR-212	Neuroprotection from A β -amyloid toxicity	Decreased levels protect from dementia	[140]
miR-218	Synaptic trafficking	Down-regulated in hyppocampal sclerosis	[151]
miR-223	Granulocyte differentiation and myeloid progenitor proliferation.	Increased in neurodegenerative conditions	[120]
miR-323-3p	Amyloid precursor protein biosynthesis	Increased in MCI	[137]
miR-382	Cell proliferation and angiogenesis	Increased in MCI	[137]
miR-384	Cell proliferation and angiogenesis	Increased in exosome from MCI patients	[143]
miR483-5p	Synaptic plasticity	Increased in different kind of dementia	[131]
miR-486-5p	Synaptic plasticity	Increased in different kind of dementia	[131]
miR-491-5p	Regulation of cell migration	Increased in MCI patients	[137]
miR-501-3p	Synaptic transmission	Decreased levels correlate with lower MMSE	[154]
miR-502-3p	Cell proliferation	Increased in different kind of dementia	[131]
miR-874	Cell proliferation	Increased in MCI patients	[137]