Human microRNA (miR-20b-5p) modulates Alzheimer's disease pathways and neuronal function, and a specific polymorphism close to the *MIR20B* gene influences Alzheimer's biomarkers.

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Supplemental Table 1. Tjur's *D* of miR-20b vs. diagnosis models

Effect	Absolute Quantitation				ΔΔCT			
	Full Model	TL[a]	CB	PCC	Full Model	TL	CB	PCC
miR-20b	0.021	0.003	0.044	< 0.001	0.024	0.117	0.048	< 0.001
*APOE*ε4 presence	0.010	0.013	0.031	< 0.001	0.085	0.191	0.098	< 0.001
Brain Region	0.004	0.029	< 0.001	< 0.001	0.091	0.150	0.144	< 0.001
*APOE*ε4 × miR-20b	< 0.001	0.001	0.005	< 0.001	0.020	0.110	0.039	< 0.001

[a]TL, CB, and PCC refer to *D* calculated on the predictions of that brain region.

Supplemental Table 2. Major AD-related proteins used as network building seeds.

Protein	Category[a]	miR-20b[b]
ADAM10	Amyloid	+
ADAM17	Amyloid	+
ADAM9	Amyloid	+
APOE	Regulator	
APP	Amyloid	+
BACE1	Amyloid	+
ECE1	Clearance	
GSK3A	Tau	
GSK3B	Tau	
IDE	Clearance	+
IL1A	Amyloid	+
IRP1	Amyloid	
IRP2	Amyloid	
MAPK13	Tau	
MAPT	Tau	+
MME	Clearance	+
PSD95	Synaptic	
PSEN1	Amyloid	
PSEN2	Amyloid	
REST	Regulator	
SNAP25	Synaptic	+
SNCA	Regulator	+
SYPH	Synaptic	

[a]Classification vs. AD relationship, specifically, Amyloid: APP, APP processing enzyme, or APP translation factor; Clearance: Aβ clearing enzyme; Regulator: Protein with functions/effects on both Aβ and hyperphosphorylated tau protein; Tau: either MAPT or one of its major kinases.

bPredicted or confirmed to interact with miR-20b-50

Supplemental Table 3. Predicted miR-20b-5p sites on VGCC subunits

Subunit	Prob[a]	ΔG
CACNA1A	no sites	no sites
CACNA1B	0.148	-17.4
CACNA1C	0.453	-19.0
CACNA1C	0.386	-16.9
CACNA1C	0.373	-15.4
CACNA1C	0.305	-17.7
CACNA1D	0.524	-14.1
CACNA1D	0.431	-20.1
CACNA1E	0.488	-16.6
CACNA1E	0.298	-14.7
CACNA1F	no sites	no sites
CACNA1G	no sites	no sites
CACNA1H	no sites	no sites
CACNA1I	0.125	-24.3
CACNA1I	0.101	-22.4
CACNA1S	no sites	no sites
CACNA2D1	0.768	-24.3
CACNA2D1	0.604	-15.8
CACNA2D1	0.550	-14.4
CACNA2D1	0.375	-13.8
CACNA2D2	0.272	-21.5
CACNA2D3	no sites	no sites
CACNA2D4	0.430	-18.8
CACNB1	0.272	-16.6
CACNB2	0.812	-19.9
CACNB2	0.463	-21.0
CACNB3	no sites	no sites
CACNB4	0.840	-19.8

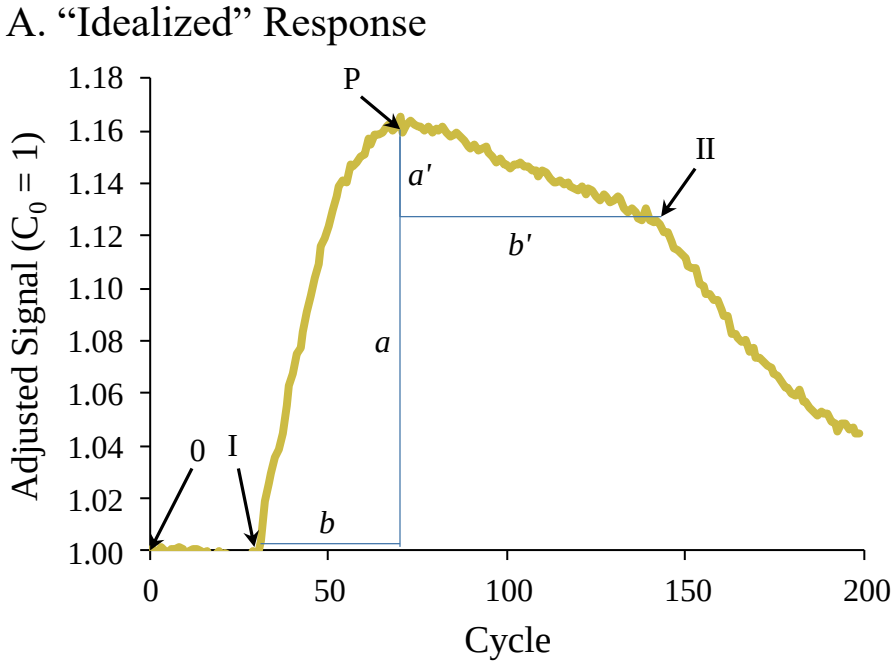
[a]Estimated probability that the sequence affinity site is likely to be a miRNA binding site.

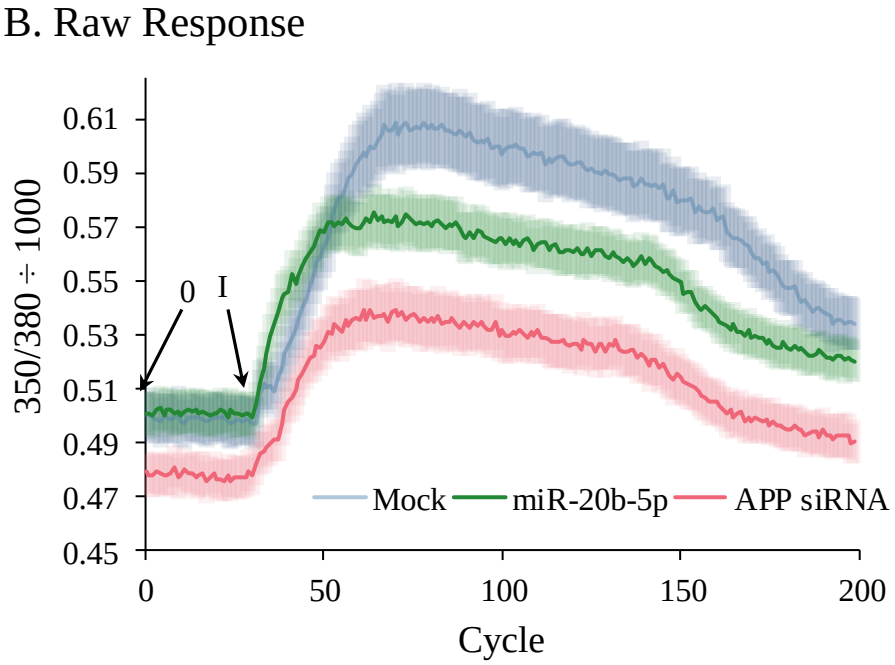
Fig. S1. Treatment with miR-20b-5p and APP siRNA alters Calcium influx. A) "Idealized" Fura response curve derived from mean of all traces. Specific points and distances of interest are described in main text. **B**) Raw mean Fura traces by treatment. **C**) Fura curves with values adjusted to the distance between "0" and "I" = 0. **D**) Fura curves scaled to minimum and maximum values for each treatment.

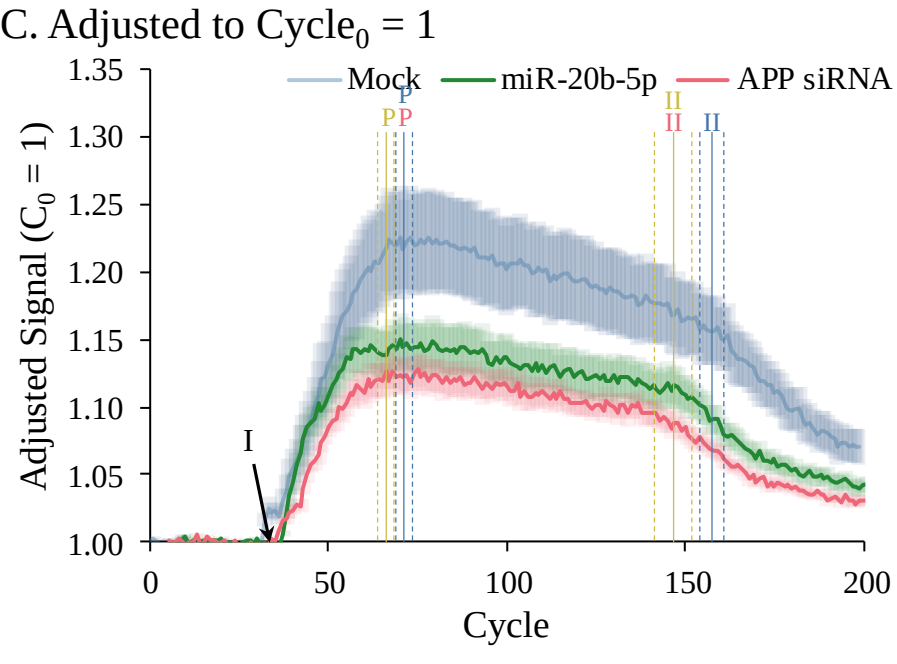
Fig. S2. Typical photomicrographs of miR-20b treatment of PHB cultures. PHB cultures were treated with miR-20b as described in the main text and grown in an incubator while photographed with the IncuCyte. Typical photographs for **A**) Mock-treated and **B**) miR-20b treated cells are shown. Apparent cell density reduction accompanied miR-20b treatment. Scales are shown on photographs.

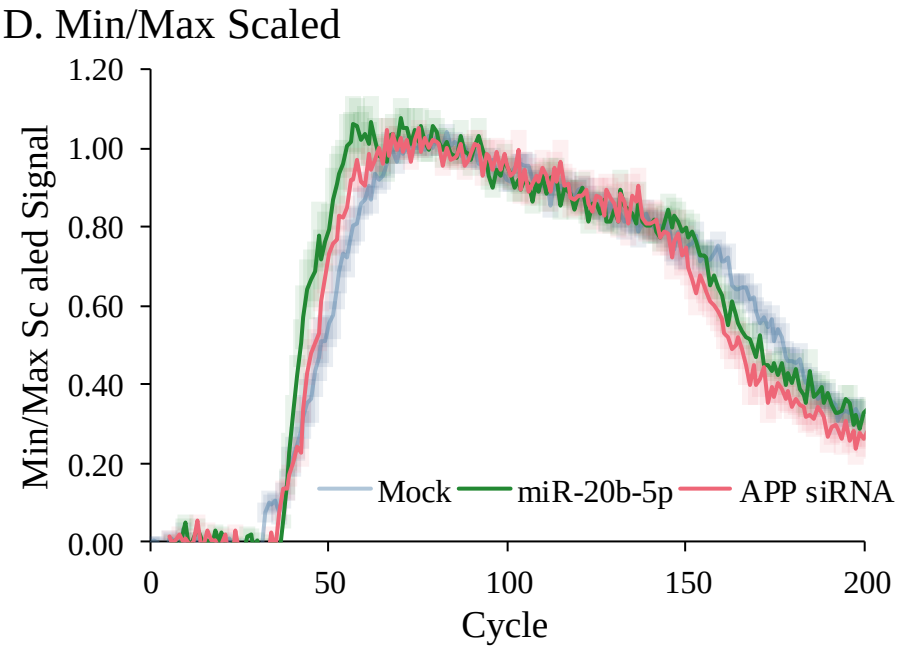
Fig. S3. Model of miR-20b-5p effects via APP on development and neurodegeneration. A proposed model that relates our data to overall neurological effects on miR-20b-5p. **A**) Under developmental downregulation, increased miR-20b-5p would downregulate APP, resulting, through different pathways, of neurological pruning. **B**) If miR-20b-5p were upregulated, this would contribute to neuroproliferation. **C**) Late in life, elevation of miR-20b-5p would effectively enhance neuropreservation primarily through reducing excitotoxic processes. **D**) Reduction of miR-20b-5p late in life would contribute to excitotoxicity through APP upregulation, leading to neurodegeneration.

S1


A. “Idealized” Response
Adjusted Signal (C_0 = 1)
Cycle
P
II
a′
b′
a
b
0
I

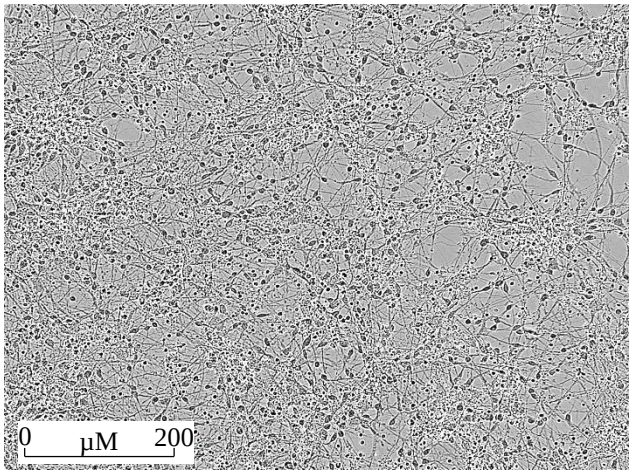

B. Raw Response
350/380 ÷ 1000
Cycle
0
I
Mock
miR-20b-5p
APP siRNA


C. Adjusted to Cycle$_0$ = 1
Adjusted Signal (C_0 = 1)
Cycle
Mock
miR-20b-5p
APP siRNA
I
P
II

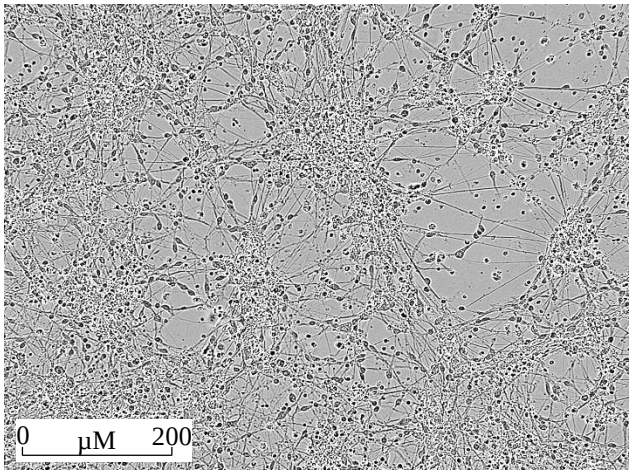

D. Min/Max Scaled
Min/Max Sc aled Signal
Cycle
Mock
miR-20b-5p
APP siRNA

S2

A. Mock

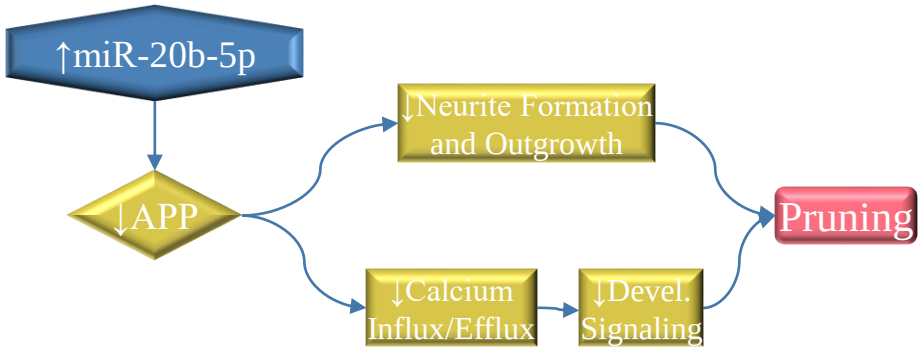


B. miR-20b

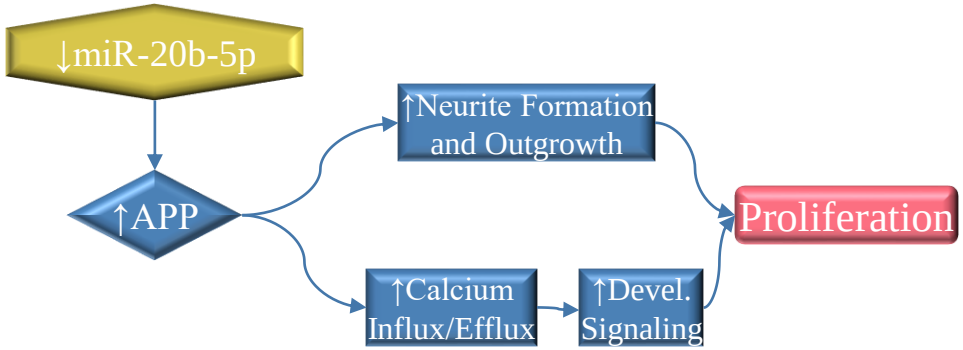


S3

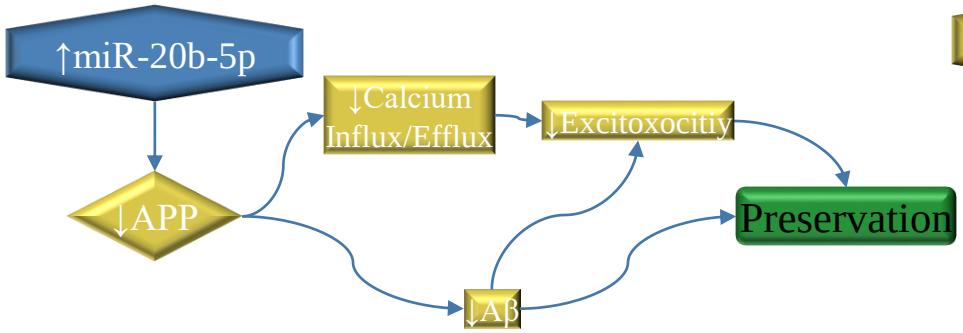
A. Developmental Downregulation



B. Developmental Upregulation



C. Late-Life Maintenance



D. Late-Life Degeneration