Evidence linking microRNA suppression of essential prosurvival genes with hippocampal cell death after traumatic brain injury

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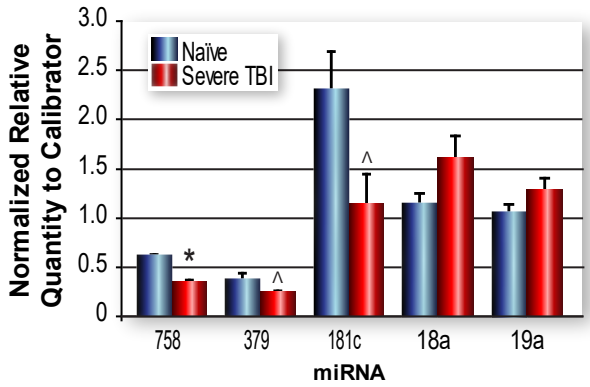
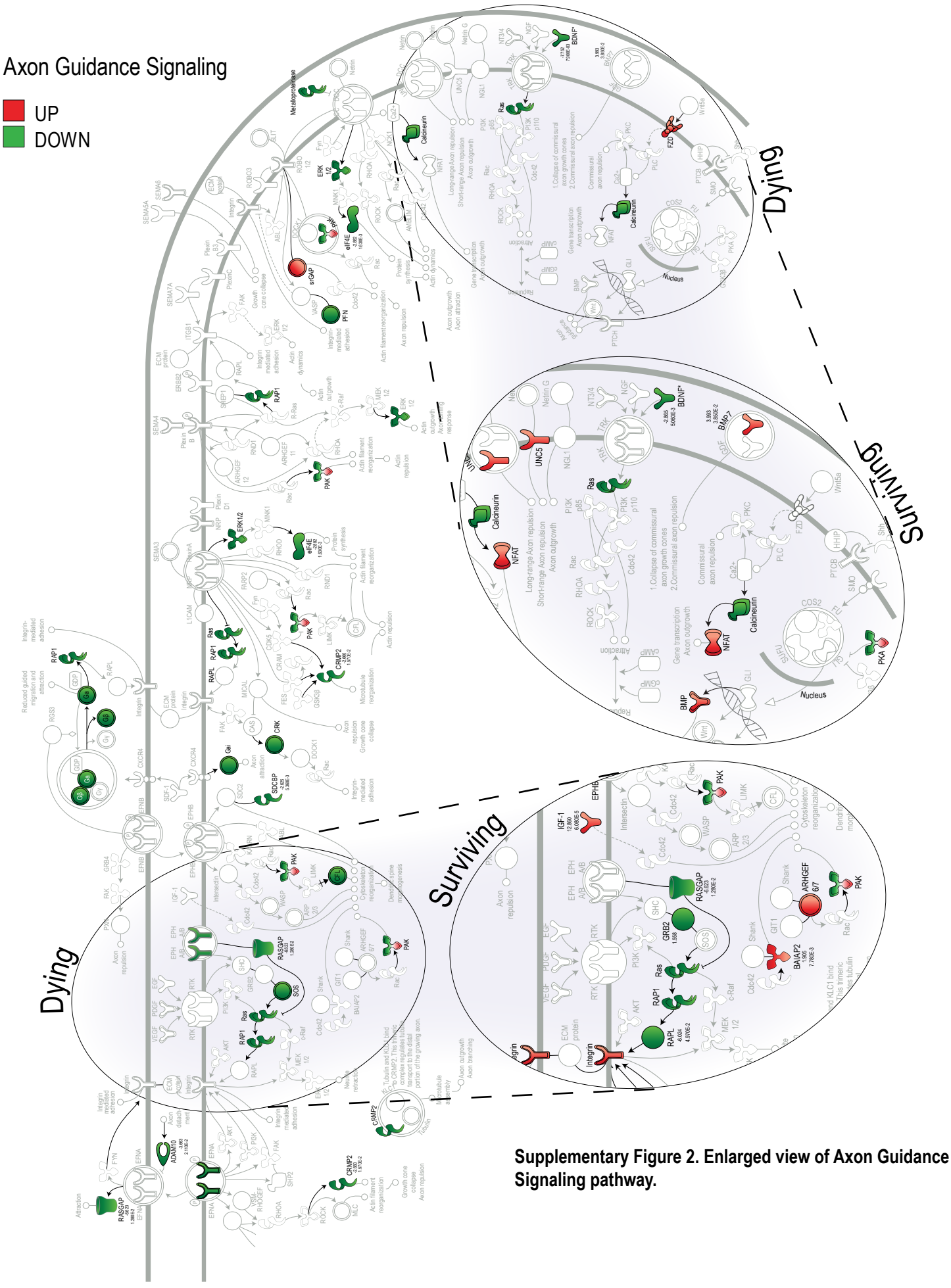
Supplementary Figure 1.



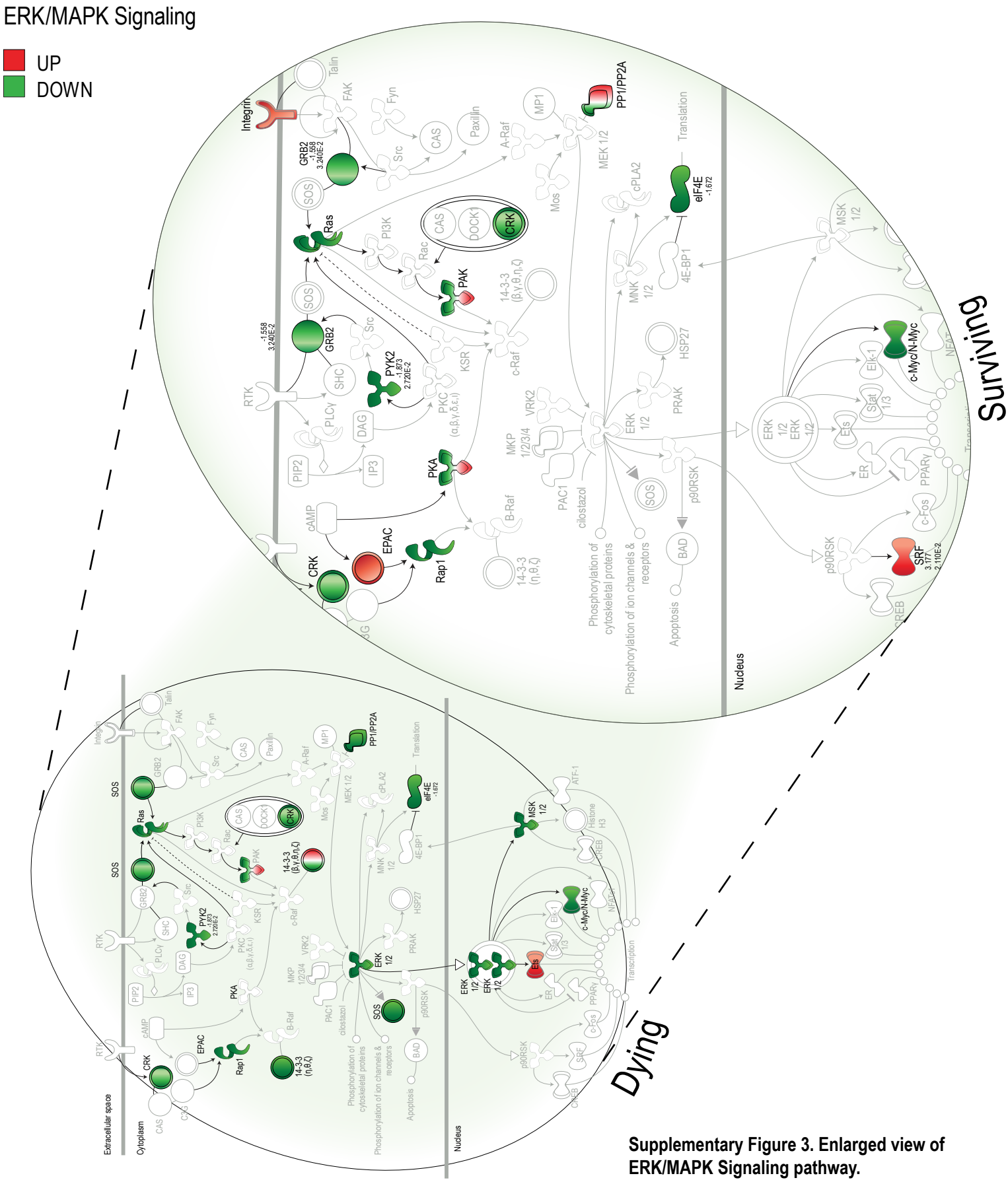
Supplementary Figure 1. Confirmation of trends in whole hippocampus microRNA microarray expression data using individual TaqMan microRNA assays. Changes in all three downregulated miRNAs (miR-181c, miR-379, miR-758) and two upregulated miRNAs (miR-181 and miR-19a) in TBI hippocampus were confirmed. Increased expression of miR-15b was independently validated by in situ hybridization (see Fig. 3 in manuscript). Differences in expression of remaining miRNAs could not be confirmed by qPCR. Total RNA and miRNA was isolated from (naïve control or TBI rat hippocampus (n=3/group) using the mirVana isolation kit (Ambion, Austin, TX). RNA was DNase-treated (Ambion). 1 ng of total RNA was assayed on an Agilent 2100 Biolanalyzer (Agilent Technologies, Santa Clara, CA) to verify each sample. Total RNA (10 ng) was reverse transcribed using the Taqman microRNA reverse transcription kit (Applied Biosystems, Life Technologies, Carlsbad, CA). Real-Time PCR was performed on an MX3000P (Stratagene, La Jolla, CA). Taqman microRNA assays were used for specific miRNA's (Applied Biosystems) with U6 as the endogenous control normalized to each miRNA. Data was analyzed with the MXPro software (Stratagene) tool using the ΔΔCT method. Students t distribution (two-tailed t-test) compared Naïve vs. Severe TBI, *P<0.05 vs. Naïve, ^ P= 0.07 vs Naive.

Supplementary Figure 2.



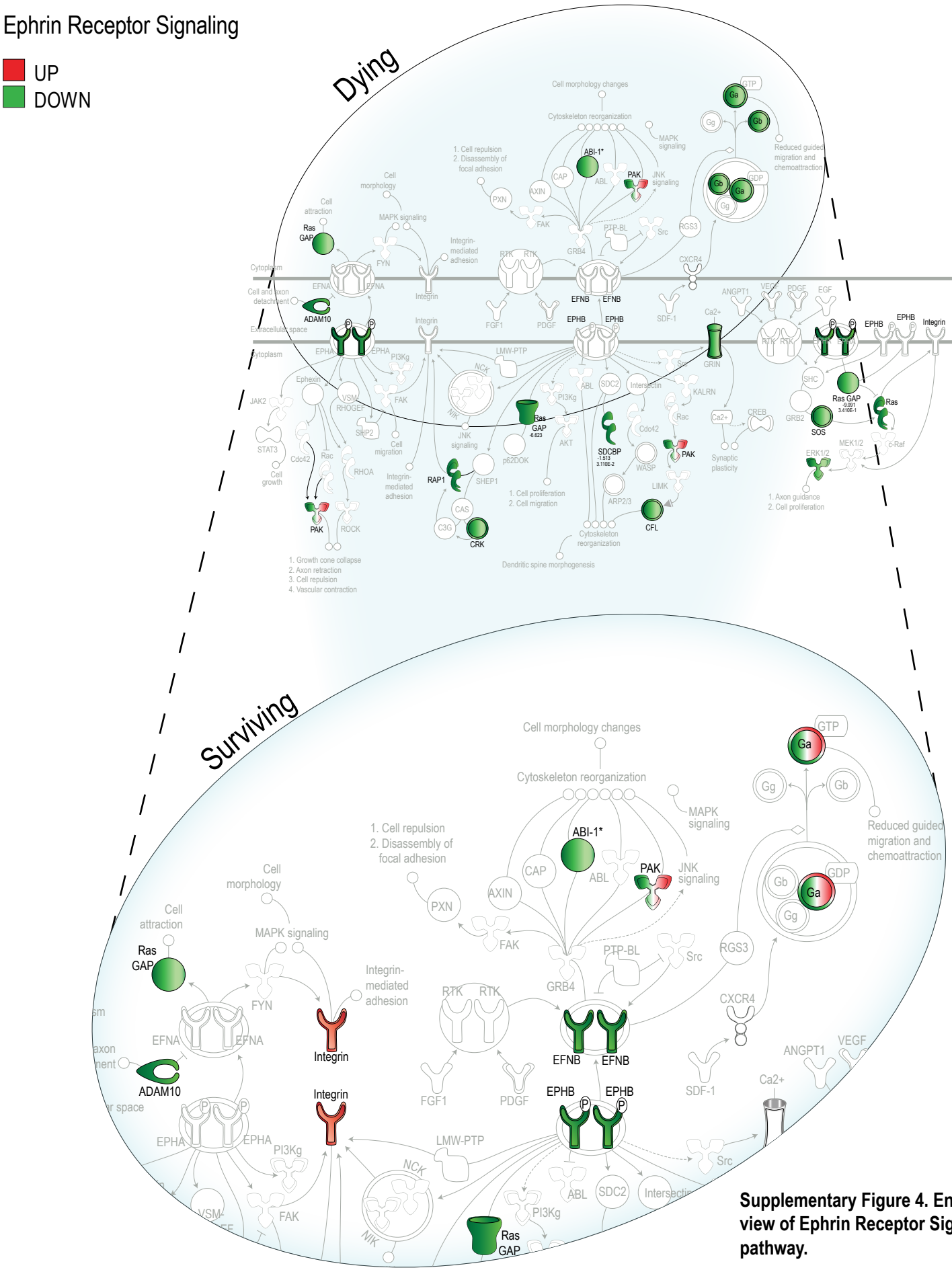
Supplementary Figure 2. Enlarged view of Axon Guidance Signaling pathway.

Supplementary Figure 3.



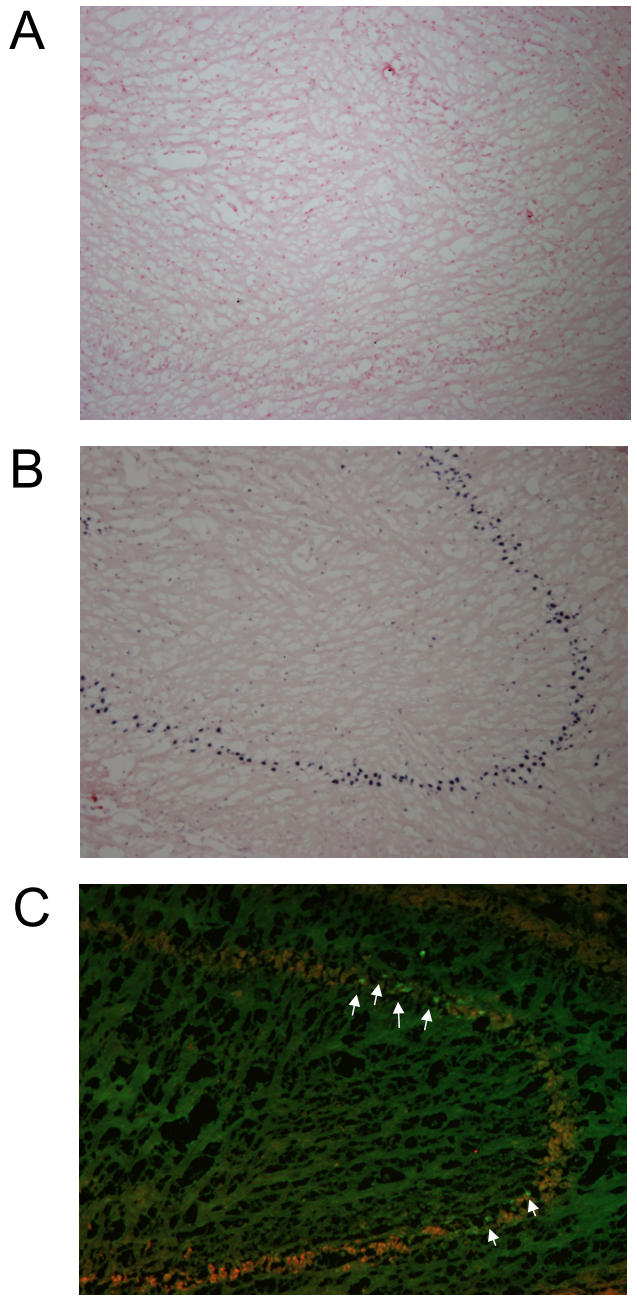
Supplementary Figure 3. Enlarged view of ERK/MAPK Signaling pathway.

Supplementary Figure 4.



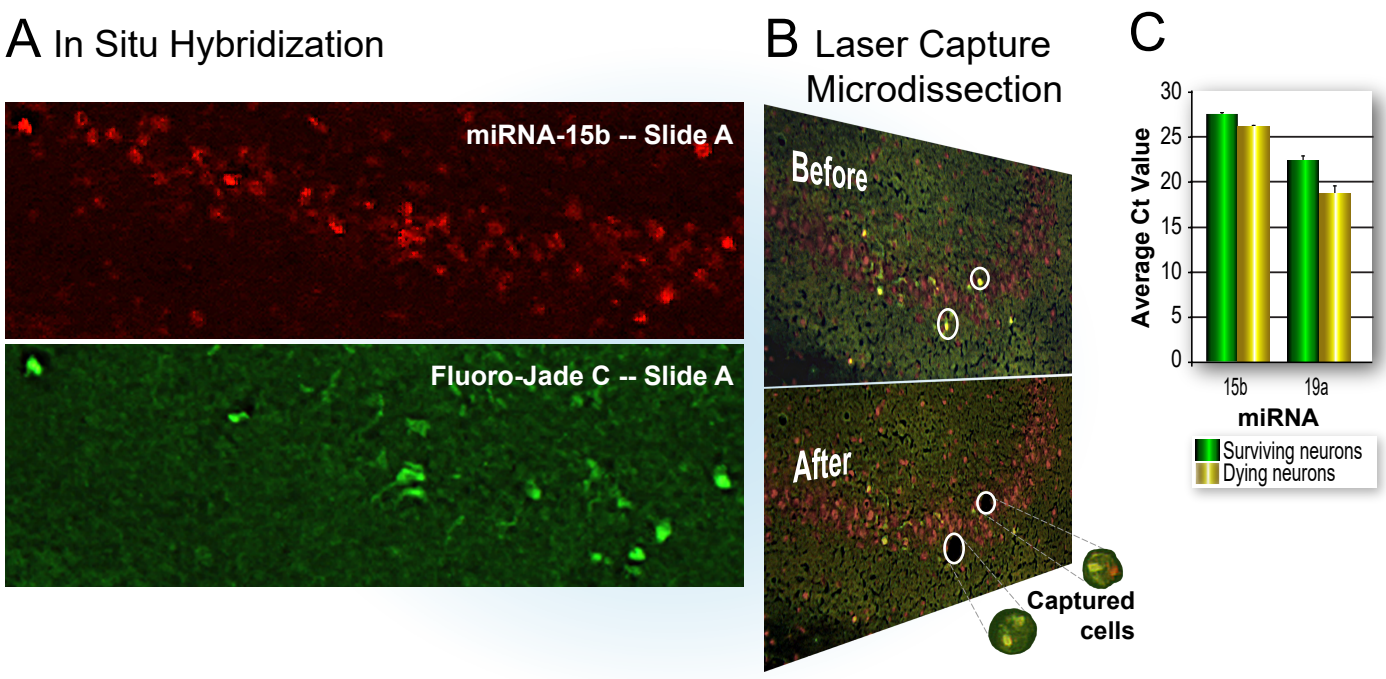
Supplementary Figure 4. Enlarged view of Ephrin Receptor Signaling pathway.

Supplementary Figure 5.



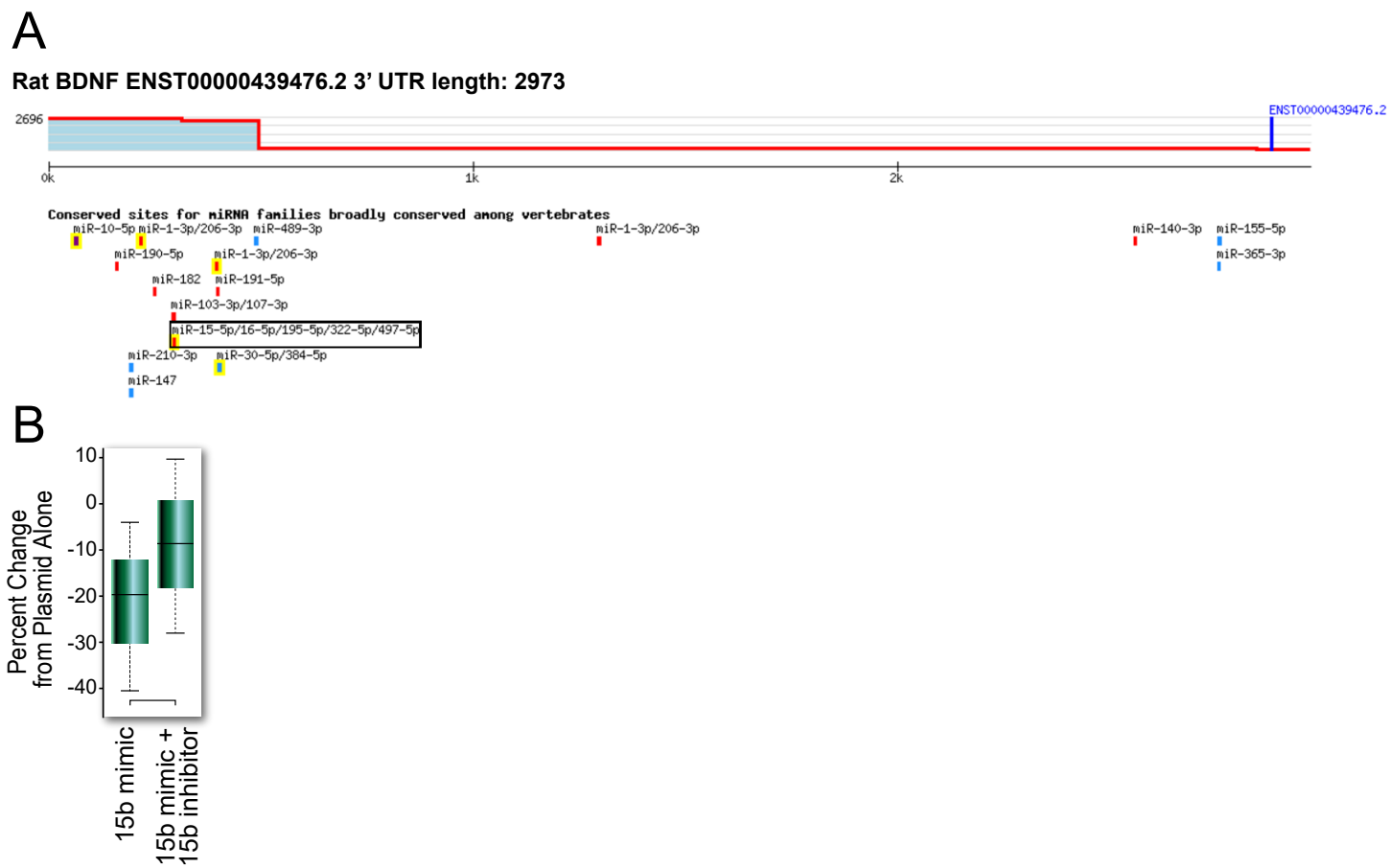
Supplementary Figure 5. In situ hybridization with locked nucleic acid scrambled and U6 probes in the hippocampal CA1, 2, and 3 pyramidal layers (A-C). In situ labeling with the scrambled probe shows non-specific binding, 10X magnification (A), anti-Digoxigenin-labeled U6 probe shows widespread labeling of pyramidal layer neurons, 10X magnification (B), and co-labeling with anti-DIG antibody to DIG-labeled U6 (red) and Fluoro Jade C (green) which is specific for dying neurons (white arrows) shows typical patterns of neurodegeneration in brain injured rats, 10X magnification (C).

Supplementary Figure 6.



Supplementary Figure 6. Analysis of microRNA expression in pools (n=6) of 30 individual cells (dying, FJ+ or surviving FJ- neurons) using Fluidigm's microfluidic 48.48 Dynamic Array integrated fluid circuit microRNA PCR chip. Total RNA containing microRNA was isolated from laser capture microdissected dying, Fluoro-Jade-positive and miR-15b positive or surviving, Fluoro-Jade-negative and miR-15b negative neurons using the RNAqueous Micro Kit (Ambion). Reverse Transcription was performed using the RT primers provided in the TaqMan MegaPlex Primer Pool A and the microRNA Reverse Transcription Kit. The resulting cDNA was then pre-amplified using the pooled Preamp primers provided in the MegaPlex kit for 15-18 cycles. The preamped products were then diluted 1:10 and 40 cycles of PCR were performed on Biomark HD system (Fluidigm Corp. San Francisco, CA). The data was analyzed using Fluidigm Real-Time Data Analysis Software. Although not statistically significant, microfluidic PCR expression levels in dying or surviving neurons trend in the same direction (lower CT values correspond to higher expression) and correlate with in situ hybridization results (Fig. 3)

Supplementary Figure 7.



Supplementary Figure 7. Evidence that miR-15b regulates brain-derived neurotrophic factor (BDNF) mRNA expression. **A.** TargetScan analysis shows that the 3' untranslated region (UTR) of BDNF contains seed binding sites for multiple brain injury dysregulated miRNAs including miR-15b. **B.** Dual luciferase reporter assays using a GenoCopoeia *Bdnf* 3'UTR construct shows that a miR-15b mimic downregulates *Bdnf* expression and a miR-15b inhibitor sequesters the miR-15b mimic and returns *Bdnf*/luciferase expression closer to control levels. Bars represent 95% confidence intervals.

Supplementary References

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