Figure S1. Research work flow.
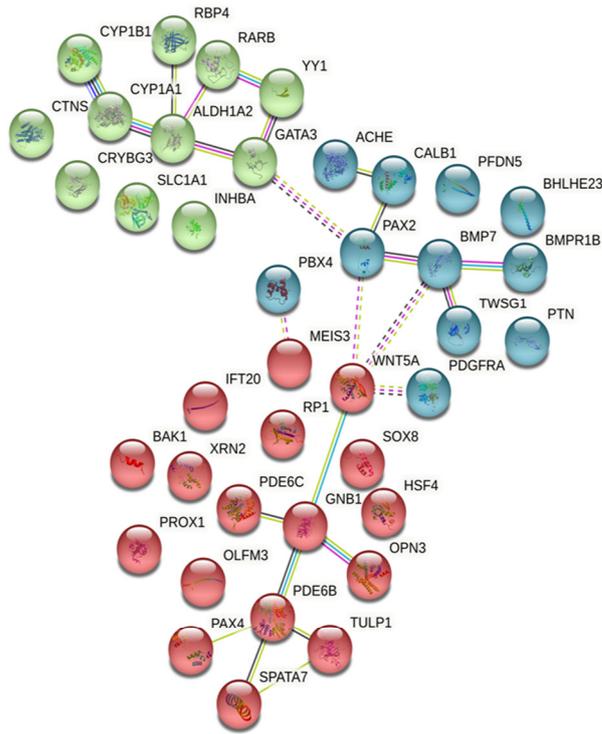
CLUSTER 1: 11 genes
PPI enrichment p-value: 1.39e-05
Biological processes
- 9-cis-retinoic acid biosynthetic process (P=0.003)
- Retinol metabolic process (FDR=3.58e-05)
- Camera-type eye development (FDR=2.00e-11)
- Secondary metabolic process (FDR=0.002)
- Lens development in camera-type eye (FDR=0.005)

CLUSTER 2: 11 genes
PPI enrichment p-value: 0.0007
Biological processes
- Embryonic camera-type eye morphogenesis (FDR=0.02)
- Retina development in camera-type eye (FDR=1.20e-09)
- Camera-type eye morphogenesis: (FDR=0.001)
- Camera-type eye development: (FDR=2.00e-11)
- Mesoderm formation (FDR=0.004)

CLUSTER 3: 17 genes
PPI enrichment p-value: 0.0003
Biological processes
- Protein localization to photoreceptor outer segment (FDR=0.01)
- Phototransduction, visible light (FDR=2.24e-06)
- Retinal rod cell differentiation (FDR=0.02)
- Retinal cone cell development (FDR=0.02)
- Camera-type eye photoreceptor cell differentiation (FDR=0.001)
- Photoreceptor cell differentiation(FDR=2.47e-08)

Uniprot annotated keywords
KW-0844: Vision (FDR= 7.75e-05)
KW-0716: Sensory transduction (FDR=0.02)
KW-0682: Retinitis pigmentosa (FDR=0.01)
KW-0238: DNA-binding (FDR=0.02)
KW-0225: Disease mutation(FDR=0.02)

Disease gene associations:
DOID:5614 Eye disease (FDR=0.0003)

Known Interactions	Predicted Interactions	Others
from curated databases	gene neighborhood	textmining
experimentally determined	gene fusions	co-expression
	gene co-occurrence	protein homology

Figure S2. Protein-protein interaction (PPI) network of differentially expressed (DE) mRNAs of RB serum exosomes related to eye development. The network was constructed using string version: 11.5. K-means clustering with minimum 3 clusters settings were applied. Three clusters were generated with 11 genes in cluster 1 (green bubbles), 11 genes in cluster 2 (blue bubbles) and 9 genes in cluster 3 (red bubbles). The selected significant biological functions for each cluster with FDR values were given. Network status: Number of nodes: 39; Number of edges: 25; Average node degree: 1.28; Avg. local clustering coefficient: 0.35; PPI enrichment p-value: 4.1e-05.
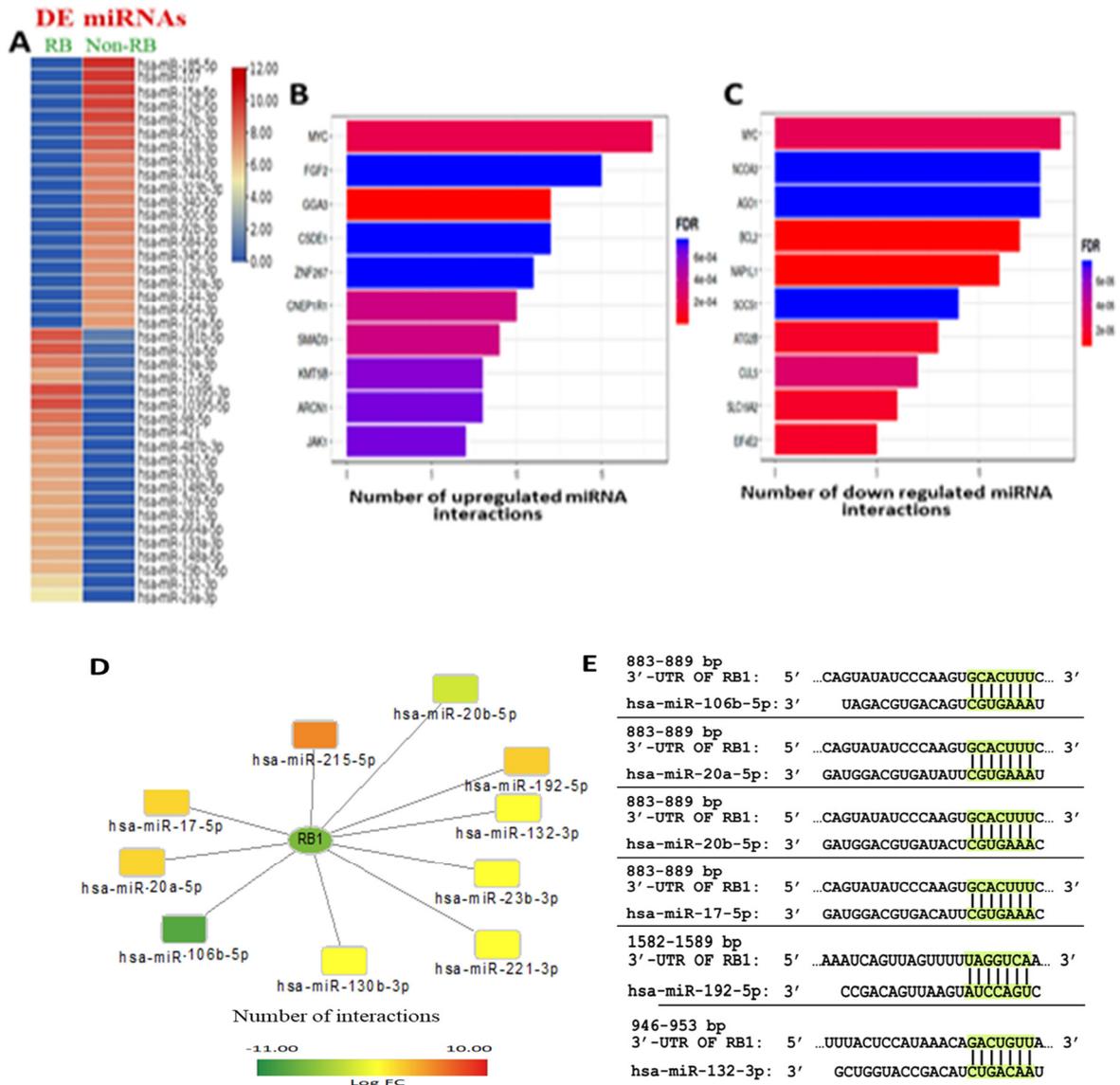
Figure S3. A. Heat map representing the differential expression of miRNAs in RB serum exosomes (sExos) vs non-RB. **B & C.** miRNA-target interactions in RB sExos for up regulated miRNAs and down regulated miRNAs. **D.** Cytoscape network depicting expression profiles of RB1 and its direct miRNA targets in RB sExos. **E.** Schematic illustration of the potential miRNA binding sites in 3′-UTRs of target RB1.
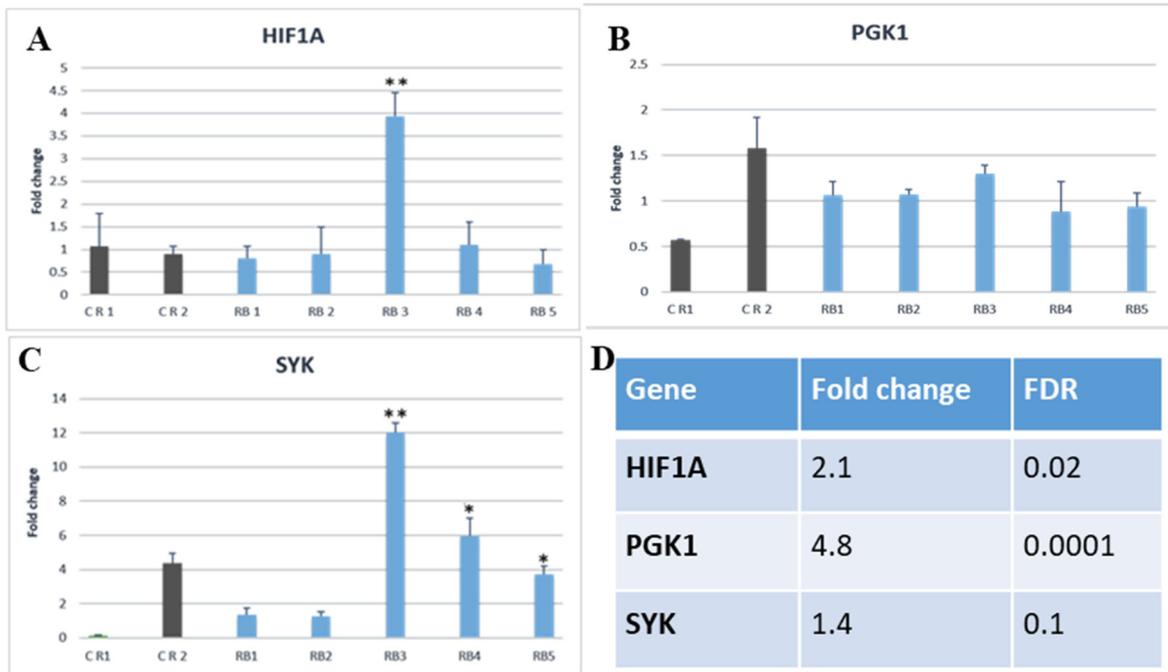
Figure S4. Real time expression data of A. HIF1A, B. PGK1, and C. SYK in primary retinoblastoma (RB) tumors and control retina (CR). *=p-value<0.05 and **=p-value<0.02 calculated by paired t test. E. RB vs non-RB serum exosomal gene expression by RNA seq.