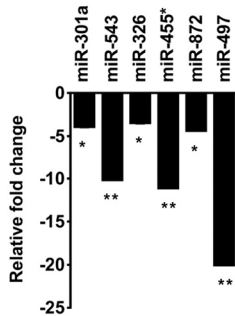
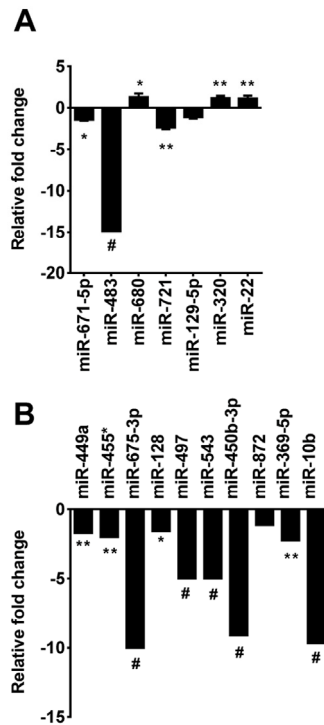


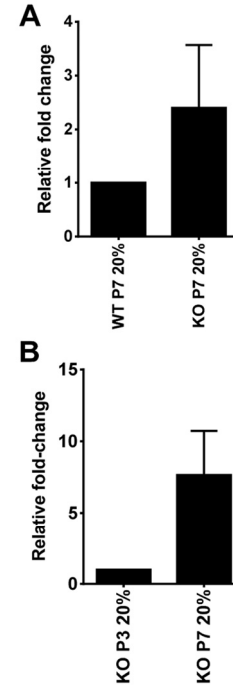
SUPPLEMENTAL DATA



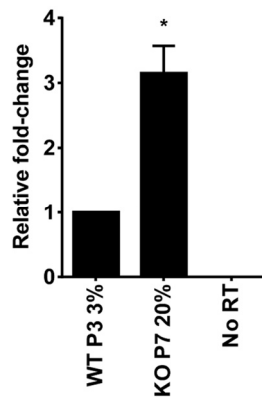
Supplemental Figure 1. QRT-PCR confirmation of downregulation of six miRNAs identified from the microarray experiments in *Ercc1*^{-/-} MEFs, compared to WT MEFs. MiRNA microarray data (Table 1) was validated by qRT-PCR analysis of *Ercc1*^{-/-} MEFs at P7 compared to WT MEFs at P7, grown to 3% O₂. WT MEFs at P7 were assigned a value of -1. Six miRNAs identified in the microarray were confirmed to be downregulated by qRT-PCR. MiR-455* refers to the less abundant miRNA product derived from the miR-455 stem-loop precursor. *P*-values were calculated using Welch's t-tests and are indicated by * (*p* < .001) and ** (*p* < .0001).



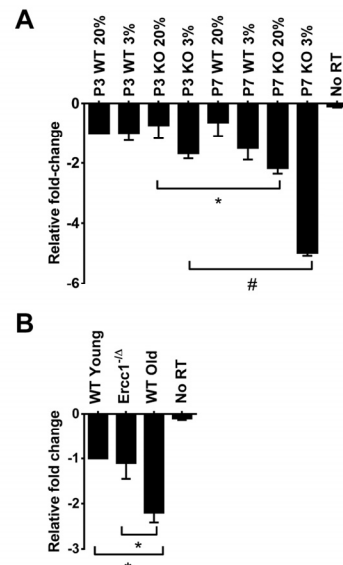
Supplemental Figure 2. QRT-PCR validation of miRNAs identified from the microarray analysis of late passage *Ercc1*^{-/-} MEFs normalized to early passage *Ercc1*^{-/-} MEFs. (A) Three miRNAs identified as being upregulated in late *Ercc1*^{-/-} MEFs compared to early passage via microarray (Table 3) were confirmed to be upregulated by qRT-PCR. QRT-PCR expression values are relative to *Ercc1*^{-/-} passage 3 samples, which were normalized to a value of either 1 or -1. (B) Ten downregulated miRNAs in P7 *Ercc1*^{-/-} MEFs from the microarray analysis (Table 3) were confirmed to be downregulated by qRT-PCR. MiR-455* refers to the less abundant miRNA product derived from the miR-455 stem-loop precursor. Expression values are relative to *Ercc1*^{-/-} passage 3 samples, which were normalized to a value of -1. *P*-values for qRT-PCR data were calculated using Welch's t-tests and are indicated by * (*p* < .05), ** (*p* < .01) and # (*p* < .0001).



Supplemental Figure 3. QRT-PCR expression of miR-467a in Passage 3 *Ercc1*^{-/-} MEFs, Passage 7 WT MEFs and Passage 7 *Ercc1*^{-/-} MEFs grown in 20% O₂. (A) MiR-467a is upregulated in *Ercc1*^{-/-} MEFs (KO) grown to Passage 7 (P7) in 20% O₂ compared to WT P7 MEFs grown to 20% O₂. QRT-PCR expression values are relative to WT P7 samples, which were normalized to a value of 1. (B) MiR-467a is upregulated in *Ercc1*^{-/-} MEFs (KO) grown to Passage 7 (P7) in 20% O₂ compared to *Ercc1*^{-/-} MEFs (KO) grown to Passage 3 in 20% O₂. Expression values are relative to *Ercc1*^{-/-} passage 3 samples, which were normalized to a value of 1. All experiments were performed in triplicate and the standard deviation is plotted as error bars.



Supplemental Figure 4. QRT-PCR expression of miR-129-5p in Passage 3 WT MEFs grown in 3% O₂ and Passage 7 *Ercc1*^{-/-} MEFs grown in 20% O₂. (A) MiR-129-5p is upregulated in late passage senescent *Ercc1*^{-/-} MEFs (KO P7) grown in 20% O₂ compared to WT Passage 3 (P3) MEFs grown in 3% O₂, which are the least senescent cells that we examined in our microarray experiments. QRT-PCR expression values are relative to WT passage 3 MEFs, which were normalized to a value of 1. All experiments were performed in triplicate and the standard deviation is plotted as error bars. *P*-values for qRT-PCR data were calculated using Welch's t-tests and are indicated by * (*p* < .05).



Supplemental Figure 5. QRT-PCR of Dicer mRNA in primary MEFs and in liver tissues shows reduced expression in senescence and aging. (A) Dicer mRNA is downregulated in Passage 7 *Ercc1*^{-/-} (P7 KO) MEFs. QRT-PCR expression values are relative to WT Passage 3 (P3 WT) samples, which were normalized to a value of 1. (B) QRT-PCR analysis was performed on livers of WT young (20 weeks), progeroid *Ercc1*^{-/-} mice (20 weeks), and WT old mice (30 months) to examine Dicer mRNA expression. Dicer mRNA is downregulated significantly in WT Old mouse livers compared to WT Young and *Ercc1*^{-/-} livers. The mean of three independent mouse livers for each condition is graphed as fold-change expression relative to WT young livers, which were normalized to a value of -1. All experiments were performed in triplicate and the standard deviation is plotted as error bars. *P*-values were calculated using Welch's t-tests and are indicated by * (*p* < .05) and # (*p* < .0001).

Supplemental Table S1. Experimentally validated target genes for miRNAs identified in this study. 3'-UTR homology between human and mouse gene orthologs was determined using Targetscan 6.2 [76].

miRNA	Target gene(s)	References
miR-10b	Bcl2l11, Hoxd10, Tfp2c	[60]
miR-128	Abcc5, Bax, Bmi1, E2F3a, E2f5, Hoxa10, Ntrk3, Reln, Ret, Rps6kb1	[65-69]
miR-449a	Bcl2, Ccnd1, Ccne2, Cdc25a, Cdk6, Dll1, E2f2, E2f3, E2f5, Gmnn, Hdac1, Hnf4a, Lef1, Met, Myc, Mycn, Notch1, Sirt1	[70]
miR-450b-3p	No confirmed mRNA targets	
miR-455*	No confirmed mRNA targets	
miR-497	Bcl2, Bcl2l2, Ccnd1, Ccnd2, Igf1r, Map2k1, Raf1	[71-73]
miR-543	Twist1	[74]
miR-872	Sod1	[75]