

# The Effect of microRNAs in the Regulation of Human *CYP3A4*: a Systematic Study using a Mathematical Model

Zhiyun Wei, Songshan Jiang, Yiting Zhang, Xiaofei Wang, Xueling Peng, Chunjie Meng, Yichen Liu, Honglian Wang, Luo Guo, Shengying Qin, Lin He, Fengmin Shao, Lirong Zhang and Qinghe Xing

## Supplemental Results

### Mathematical model for miRNA function

The simplified model of miRNA action was schematically shown in Figure S3. The *CYP3A4* mRNA was produced with a transcription rate  $\tau_m$  and decayed with a rate  $\delta_m$ . Similarly, the miRNA was produced with a rate  $\tau_s$  and decayed with a rate  $\delta_s$ . mRNA and miRNA reversibly bound together to form the complex, with a forward rate  $\beta$  and a reverse rate  $\beta^-$ . The *CYP3A4* protein was produced with a translation rate  $\lambda$  from free mRNA and decayed with a rate  $\delta_p$ .

In the steady state, we had four formulas as follows:

$$\begin{aligned}\frac{dc_{fm}}{dt} &= \tau_m - \delta_m c_{fm} - \beta c_{fm} c_{fs} + \beta^- c_c = 0; \\ \frac{dc_{fs}}{dt} &= \tau_s - \delta_s c_{fs} - \beta c_{fm} c_{fs} + \beta^- c_c = 0; \\ \frac{dc_c}{dt} &= \beta c_{fm} c_{fs} - \beta^- c_c = 0; \\ \frac{dc_p}{dt} &= \lambda c_{fm} - \delta_p c_p = 0.\end{aligned}$$

Considering that the total RNA was denatured during extraction, the concentrations of mRNA and miRNA were actually  $c_m = c_{fm} + c_c$  and  $c_s = c_{fs} + c_c$ , respectively. The concept of

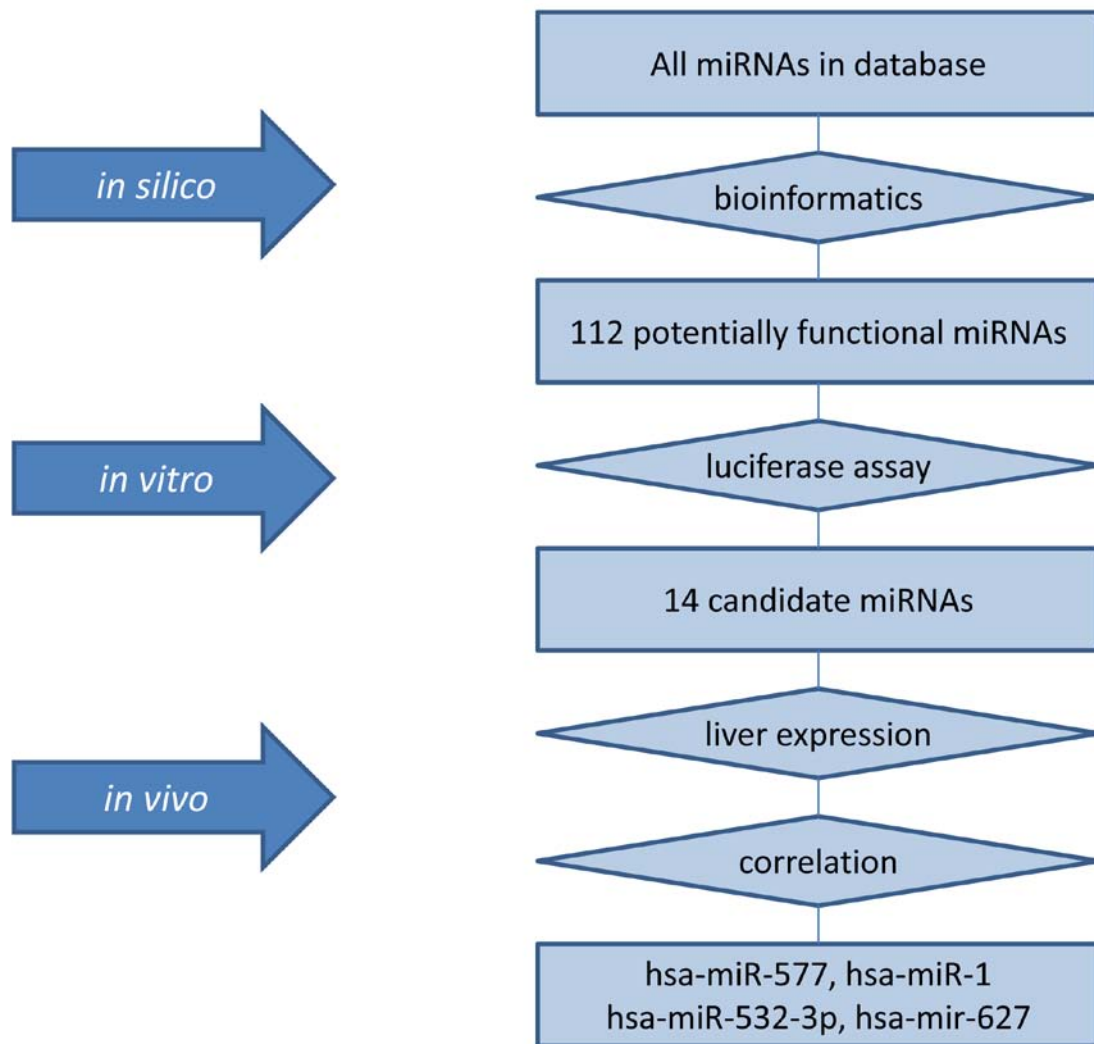
“translation efficiency”,  $e_{translation} = \frac{c_p}{c_m}$ , was used here to assess the influence of miRNA, as the

previous investigation<sup>20</sup>. Solving above equations, we could discover the relationship between the translation efficiency and the concentration of miRNA as

$$\frac{1}{e_{translation}} = \frac{c_m}{c_p} = \frac{\delta_p}{\lambda} + \frac{\beta \delta_p}{\lambda} \frac{\delta_m}{\beta^- \delta_m + \beta \tau_m} c_s = A + B \cdot c_s,$$

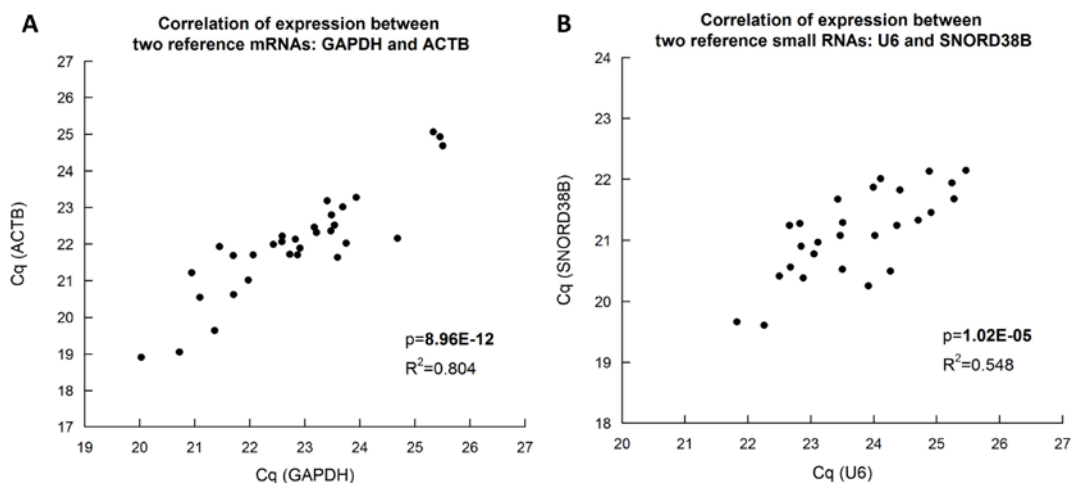
where  $A$  and  $B$  represented constants. It was convenient for researchers to evaluate significance of miRNA effect using such linear correlation.

**Supplemental Figure S1.** Flow chart of our systematic study for influence of miRNAs on *CYP3A4* expression.



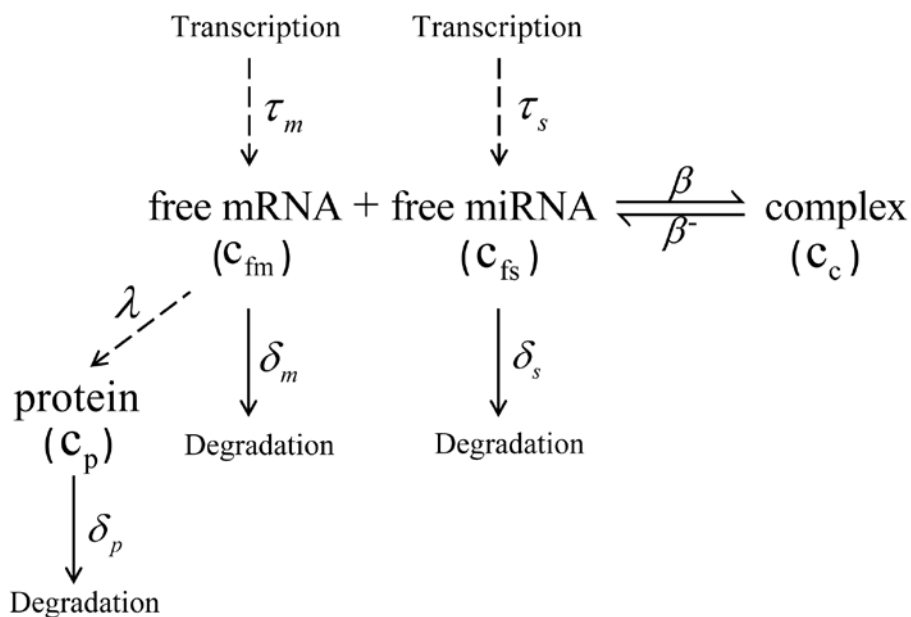
**Supplemental Figure S2.** Correlation of the expression of two reference genes.

There are significant correlations between the expression of two reference mRNAs (GAPDH and ACTB; A) and two reference small RNAs (U6 and SNORD38B; B).



**Supplemental Figure S3.** Biochemistry involved in our model for microRNA function.

Solid arrows represent chemical reactions, while dotted arrows represent guiding synthesis without consumption of the reactant.



**Supplemental Table S1.** Relative luciferase ratio of miRNAs which were predicted by at least one of three prediction software.

miRNA	T	M	D	Relative luciferase ratio (Normalized to the empty vector)	p value
hsa-miR-27b	+	-	+	0.544	0.018
hsa-miR-627	+	-	+	0.656	0.016
hsa-miR-653	-	-	+	0.672	0.006

hsa-miR-660	-	+	-	0.684	0.006
hsa-miR-934	-	+	-	0.714	0.064
hsa-miR-361	+	+	+	0.718	0.014
hsa-miR-613	+	-	-	0.719	0.008
hsa-miR-219-5p	-	+	-	0.720	0.050
hsa-miR-526b	+	-	-	0.739	0.020
hsa-miR-569	+	+	+	0.740	0.001
hsa-miR-548a	+	+	+	0.761	0.019
hsa-miR-582-3p	-	-	+	0.763	0.044
hsa-miR-1	+	-	+	0.764	0.013
hsa-miR-629	+	-	-	0.769	0.008
hsa-miR-532-3p	-	-	+	0.773	0.010
hsa-miR-374	+	-	+	0.787	0.066
hsa-miR-559	+	-	+	0.790	0.006
hsa-miR-578	+	-	-	0.794	0.057
hsa-miR-577	-	+	-	0.800	0.006
hsa-miR-609	+	-	+	0.803	0.059
hsa-miR-637	+	-	+	0.807	0.014
hsa-miR-548c-5p	-	+	+	0.838	0.063
hsa-miR-488	-	+	+	0.838	0.099
hsa-miR-579	+	-	+	0.839	0.144
hsa-miR-873	-	-	+	0.842	0.122
hsa-miR-208	+	-	-	0.848	0.060
hsa-miR-508-5p	-	+	+	0.859	0.168
hsa-miR-31	+	-	-	0.864	0.138
hsa-miR-765	+	-	+	0.864	0.106
hsa-miR-142-3p	+	-	+	0.880	0.052
hsa-miR-499	+	+	+	0.883	0.108
hsa-miR-550	-	-	+	0.885	0.036
hsa-miR-659	+	-	+	0.895	0.055
hsa-miR-133b	-	-	+	0.899	0.374
hsa-miR-543	-	-	+	0.902	0.103
hsa-miR-511	+	-	-	0.921	0.260
hsa-miR-766	-	-	+	0.921	0.337
hsa-miR-517*	-	+	-	0.921	0.197
hsa-miR-520a-5p	-	-	+	0.924	0.084
hsa-miR-525	+	-	+	0.926	0.258
hsa-miR-580	+	-	+	0.928	0.371
hsa-miR-518a-5p	-	+	-	0.928	0.165
hsa-miR-342-3p	+	-	+	0.951	0.257

hsa-miR-519d	+	-	-	0.956	0.484
hsa-miR-570	-	-	+	0.958	0.299
hsa-miR-411	+	-	+	0.960	0.089
hsa-miR-648	-	-	+	0.963	0.260
hsa-miR-520g	-	-	+	0.964	0.293
hsa-miR-616	-	-	+	0.969	0.364
hsa-miR-429	+	-	+	0.971	0.422
hsa-miR-491-3p	-	-	+	0.983	0.303
hsa-miR-206	+	-	+	0.989	0.463
hsa-miR-26a	+	-	+	0.998	0.130
hsa-miR-410	-	-	+	1.014	0.444
hsa-miR-326	+	-	-	1.021	0.405
hsa-miR-133a	-	-	+	1.024	0.382
hsa-miR-196a	-	+	-	1.025	0.258
hsa-miR-453	-	+	-	1.053	0.297
hsa-miR-106a	+	-	-	1.054	0.014
hsa-miR-944	-	-	+	1.065	0.273
hsa-miR-335*	-	+	-	1.066	0.071
hsa-miR-25	-	-	+	1.075	0.019
hsa-miR-576	+	-	-	1.076	0.061
hsa-miR-17-5p	+	-	-	1.078	0.015
hsa-miR-26b	+	-	+	1.084	0.090
hsa-miR-892a	-	-	+	1.085	0.297
hsa-miR-593	-	-	+	1.090	0.282
hsa-miR-216	+	-	-	1.092	0.038
hsa-miR-122	+	-	+	1.096	0.039
hsa-miR-455-3p	-	+	+	1.097	0.081
hsa-miR-655	-	-	+	1.098	0.337
hsa-miR-548d-5p	-	+	+	1.101	0.262
hsa-miR-608	+	+	+	1.103	0.175
hsa-miR-921	-	-	+	1.109	0.077
hsa-miR-520h	-	-	+	1.115	0.087
hsa-miR-106b	+	-	+	1.121	0.037
hsa-miR-141	+	-	+	1.131	0.193
hsa-miR-374b	-	-	+	1.140	0.037
hsa-miR-224	+	-	+	1.149	0.019
hsa-miR-181a*	-	+	-	1.163	0.009
hsa-miR-505	+	-	-	1.166	0.011
hsa-miR-452	-	-	+	1.182	0.000
hsa-miR-599	+	-	-	1.193	0.041

hsa-miR-200b	+	-	+	1.206	0.022
hsa-miR-421	+	-	-	1.211	0.041
hsa-miR-330-3p	+	+	+	1.224	0.011
hsa-miR-494	+	-	+	1.255	0.039
hsa-miR-369-3p	+	-	+	1.256	0.118
hsa-miR-652	-	+	-	1.261	0.115
hsa-miR-150	+	-	+	1.276	0.000
hsa-miR-192	-	-	+	1.291	0.002
hsa-miR-423-5p	-	+	-	1.296	0.022
hsa-miR-20a	+	-	+	1.296	0.010
hsa-miR-128a	+	-	+	1.304	0.122
hsa-miR-200a	+	-	+	1.310	0.036
hsa-miR-138-1*	-	+	-	1.315	0.027
hsa-miR-203	+	-	-	1.324	0.073
hsa-miR-138-2*	-	+	-	1.365	0.009
hsa-miR-595	+	-	-	1.389	0.000
hsa-miR-548b-5p	-	+	+	1.429	0.086
hsa-miR-409-3p	-	-	+	1.431	0.014
hsa-miR-941	-	-	+	1.456	0.058
hsa-miR-20b	+	-	-	1.483	0.004
hsa-miR-140-5p	-	-	+	1.499	0.007
hsa-miR-539	+	+	+	1.531	0.010
hsa-miR-24	+	-	+	NA	NA
hsa-miR-27a	+	-	+	NA	NA
hsa-miR-152	-	-	+	NA	NA
hsa-miR-200c	+	-	+	NA	NA
hsa-miR-377*	-	+	-	NA	NA
hsa-miR-378	+	-	-	NA	NA
hsa-miR-431	+	-	+	NA	NA

---

T: TargetScan; M: miRbase; D: DIANA; NA: not available in our miRNA library.