Statin's Effect on Oncogenic miRNAs in Hematologic Malignancy Patients

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Background

Statins, the 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are commonly used as potent inhibitors for cholesterol synthesis. Particularly, statins are essential for the treatment of lipid disorders and for cardiovascular disease prevention (1). Convincing evidence has demonstrated the pleiotropic effects of reducing cellular cholesterol precursor, mevalonic acid, on improving the immune system and cancer prevention in hematological malignancies (2,3). However, contrary to the original understanding of the biological effect of statins, recent studies have shown that the benefits of statin are not solely mediated by their lipid-lowering properties (4). Several studies have pointed out miRNA's potential as biomarkers for drug response and clinical outcome prediction, as well as promising therapeutic targets in HM (5,6). In this study we examined the effect of statin on these miRNAs in HM patients and used the data to predict the different pathways that are influenced by this treatment.

	Pretreatment ΔCT		Posttreatment ΔCT				
	Mean	SD	Mean	SD	Fold Change	Trend	P value
miR-198	-0.43	3.66	-4.03	2.70	12.10	Up regulation	0.0062
let-7-family	-0.21	2.48	-3.48	5.49	9.64	Up regulation	0.0557
miR-29a+b+c	1.71	2.57	-1.42	2.43	8.77	Up regulation	0.0060
miR-204	-2.09	3.54	-5.17	3.00	8.44	Up regulation	0.0015
miR-222	-0.37	2.66	-2.98	2.48	6.09	Up regulation	0.0194
miR-224	4.71	3.45	2.24	2.67	5.53	Up regulation	0.0060
miR-155	0.62	2.42	-1.69	3.04	4.97	Up regulation	0.0209
miR-128b	3.50	2.85	1.20	2.99	4.96	Up regulation	0.0442
miR-296	-1.09	2.87	-2.99	2.38	3.75	Up regulation	0.0459
miR-199a+b	0.61	2.82	-1.24	2.48	3.61	Up regulation	0.0493
miR-194	0.03	1.91	-1.78	2.67	3.51	Up regulation	0.0439
miR-125a	-5.26	1.73	-7.04	2.39	3.44	Up regulation	0.0148
miR-200a	1.41	2.30	0.11	2.26	2.46	Up regulation	0.0112
miR-150	-6.44	3.03	-4.20	3.35	0.21	Down regulation	0.0500

Table 1: Pre and post atorvastatin treatment expression of differentially expressed miRNAs

Objective

To identify significantly differentially expressed miRNAs and involved regulatory pathways post atorvastatin treatment in HM patients.

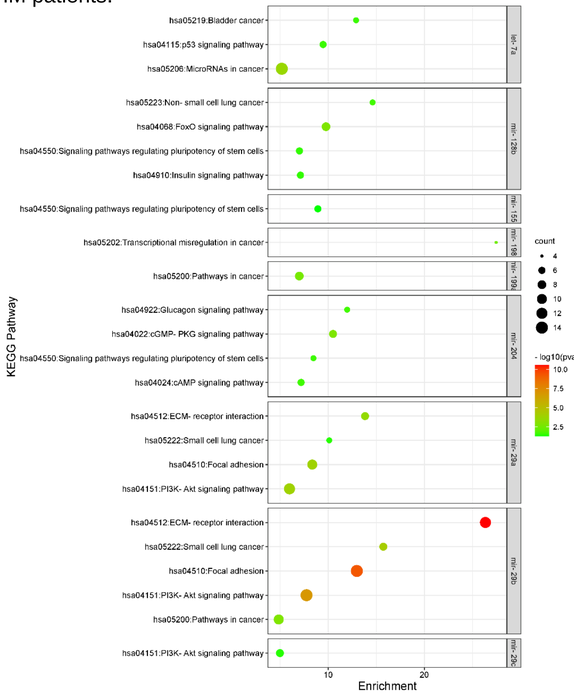


Figure 2: Bubble charts demonstrating enriched KEGG Pathways in predicted target genes for differentially expressed miRNAs

Materials & Methods

A panel of 95 plasma circulating miRNAs involved in tumorigenesis, apoptosis, and differentiation were relatively quantified using qPCR for blood samples obtained from 12 HM patients, 4 with chronic myeloid leukemia, 4 with non-Hodgkin lymphoma, and 4 with essential thrombocythemia. Pre- and post-administration of a 6-week atorvastatin course miRNA expression levels were measured. Significantly differentially expressed miRNAs were those with a fold change > 2 or < 0.5 using the Livak method with a two-sided P value < 0.05. To further understand the underlying mechanism of statin, regulated differentially GO and KEGG pathway enrichment analyses were conducted for identified target genes using the DAVID 6.8 bioinformatics tool.

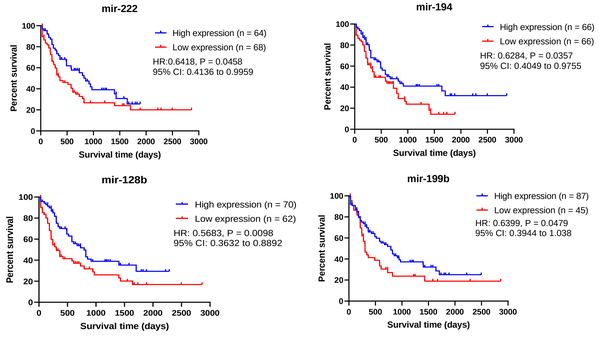


Figure 1: Overall survival curves demonstrating the prognostic value of significant differentially expressed miRNAs in acute myeloid leukemia (AML) patients from The Cancer Genomic Atlas. Patients were stratified into high and low expression groups using the median expression as a cutoff point. Overall survival curves were plotted using the Kaplan Meier method and comparison between high and low expression cohorts was done using the log-rank test.

Results

Out of 95, 14 miRNAs exhibited significant fold changes post-treatment with statins including miR-198, miR-29a+b+c, miR-204, miR-222, miR-224, miR-155, miR-128b, miR-296, miR-199a+b, miR-194, miR-125a, miR-200a, and the let-7-family that were upregulated and miR-150 that was downregulated post statin treatment (**Table 1**). Higher mir-222, mir-194, mir-128b and mir-199b expressions were significantly associated with better overall survival using the Cancer Genomic Atlas leukemia and lymphoma patient cohorts (**Figure 1**). Enrichment analysis identified the PI3k-Akt pathway as well as other pathways involved in epithelial-mesenchymal transition (**Figure 2**).

Conclusion

Atorvastatin upregulated several tumor suppressor genes involved in mediating better prognosis. These findings provide deeper insight on statin's effect on the transcriptional regulatory level in cancer which can be used to enhance personalized treatment options for HM patients. Further studies on larger homogeneous samples are needed to confirm the long-term effects of adding statins to HM standard lines of therapy.

References

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