

Expression patterns of microRNAs and associated target genes in ulcerated primary cutaneous melanoma

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COMPREHENSIVE CANCER CENTER

Emily Schwarz^{1*}, Mallory J. DiVincenzo DVM^{1,2*}, Casey Ren MD¹, Zoe Barricklow¹, Maribelle Moufawad¹, Lianbo Yu PhD¹, Paolo Fadda PharmD¹, Colin Angell¹, Steven Sun MD¹, Sara Zelinskas¹, J. Harrison Howard MD¹, Catherine Chung MD¹, Craig Slingluff MD³, Alejandro A. Gru MD⁴, Kari Kendra MD¹, William E. Carson MD¹

¹The Arthur G. James Cancer Hospital and Solove Research Institute, The Ohio State University, Columbus, OH, ²Department of Veterinary Biosciences, The Ohio State University, Columbus, OH, ³Division of Surgical Oncology, University of Virginia, Charlottesville, VA, ⁴Department of Pathology, University of Virginia, Charlottesville, VA

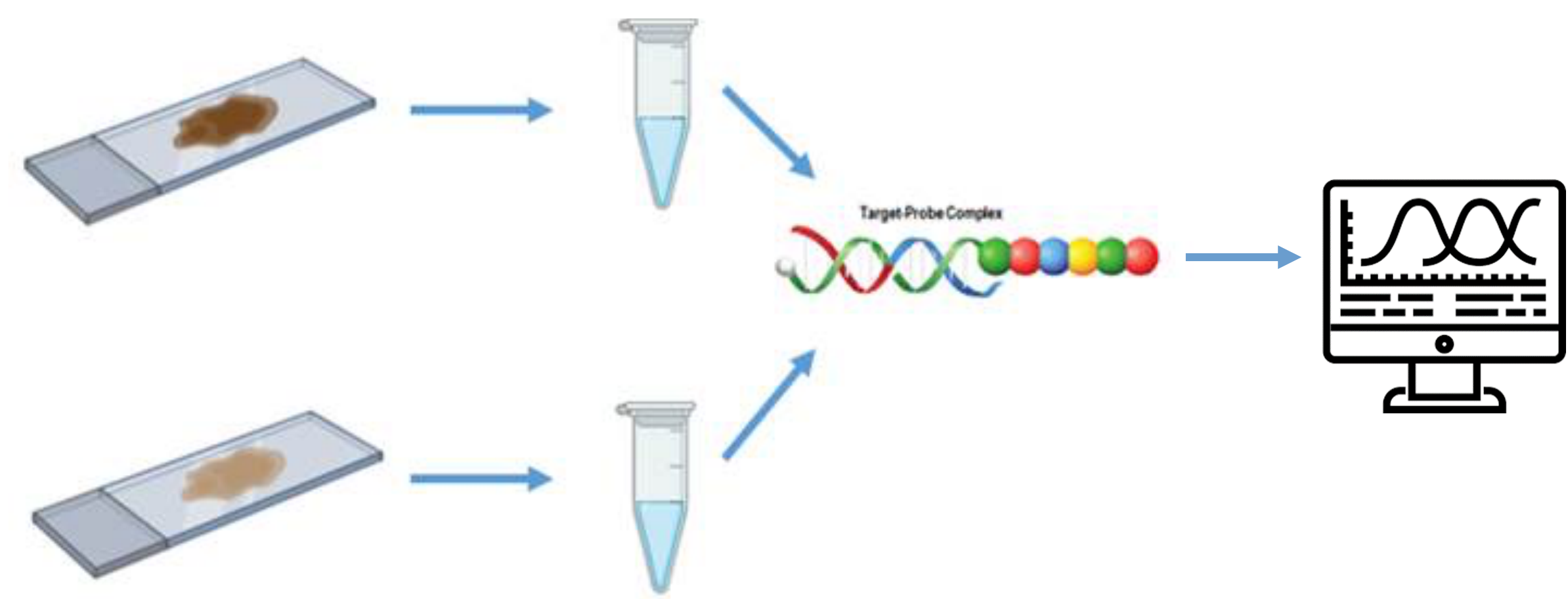
Background

- Melanoma is estimated to result in 7,650 deaths in the United States alone this year
- Cutaneous melanoma can present with tumor ulceration correlating with higher metastatic risk and poorer prognosis compared to non-ulcerated tumors
- MicroRNAs (miRs) are short, non-coding RNAs averaging 22 nucleotides that regulate gene expression via post-transcriptional regulation
- Multiple miRs have been identified as dysregulated in melanoma and miR expression in tumor tissue has been shown to be predictive of responses to therapy and metastatic progression
- However, expression patterns and effects of miRs in melanoma tumor ulceration remains largely unexplored

Hypothesis: A unique microRNA profile exists in ulcerated relative to non-ulcerated melanoma, and that microRNA expression inversely correlates with target genes of biologic importance.

Methods

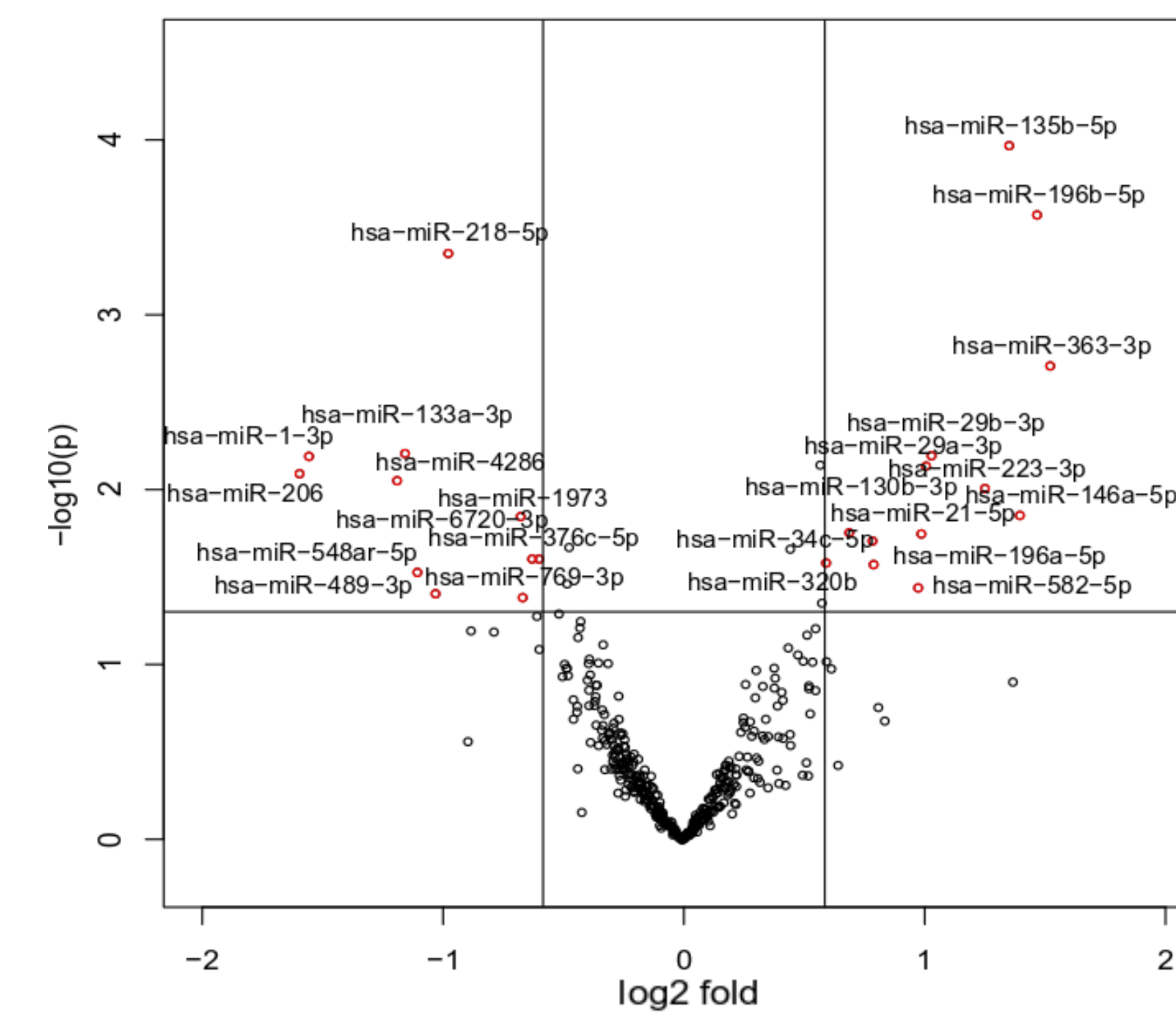
- miR/mRNA expression was assessed in ulcerated and non-ulcerated cutaneous melanomas (n=35) using NanoString Human miRNA and Tumor Signaling 360 mRNA assays and validated in an independent cohort (n=12)



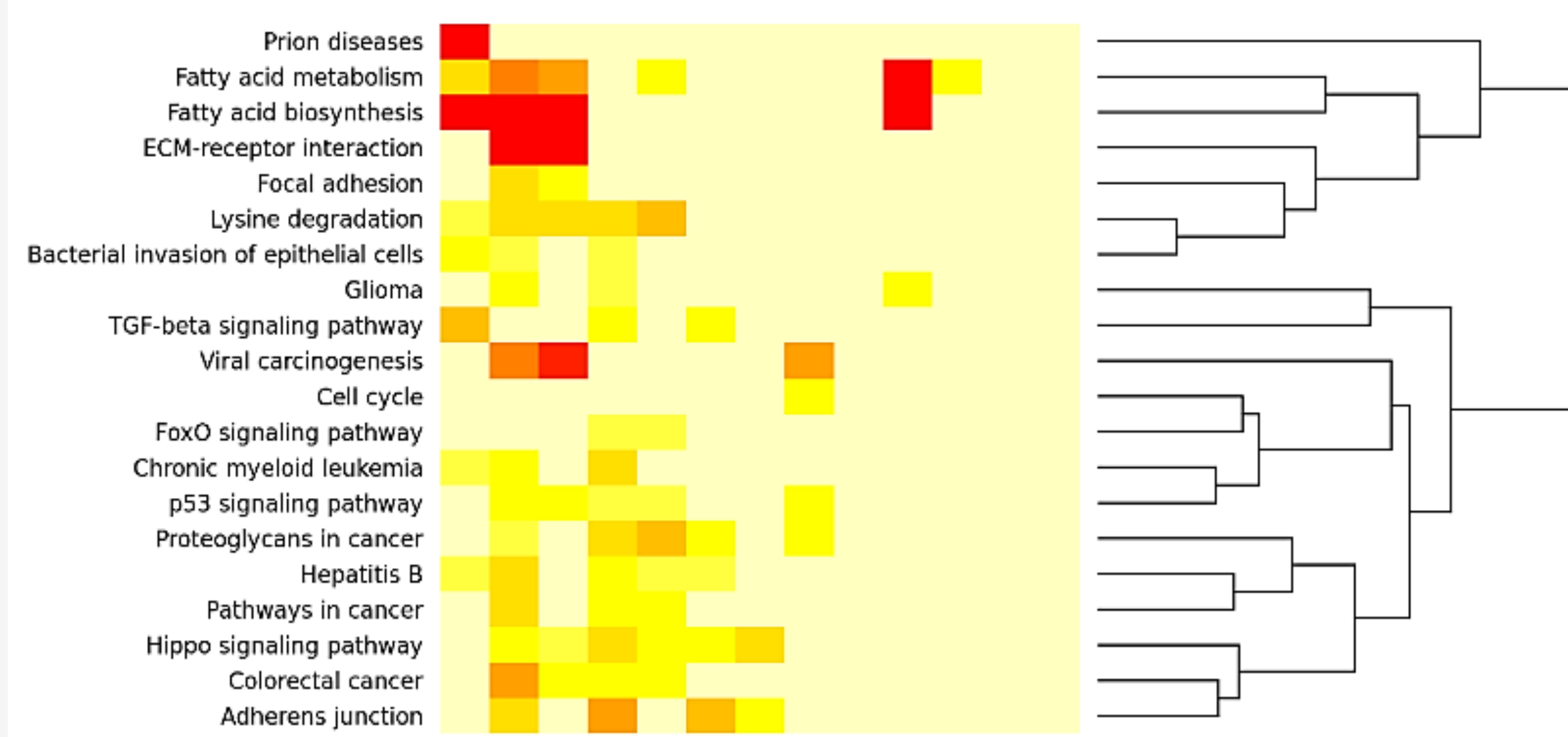
- Linear models and a moderated t-test were used to detect differential expression between ulcerated and non-ulcerated tumors
- Pearson correlations were used to predict potential miR-mRNA binding pairs. Differentially expressed mRNA transcripts in ulcerated melanoma were identified as predicted or validated targets of individual miRs using Ingenuity Pathway Analysis miRNA target filter

Results

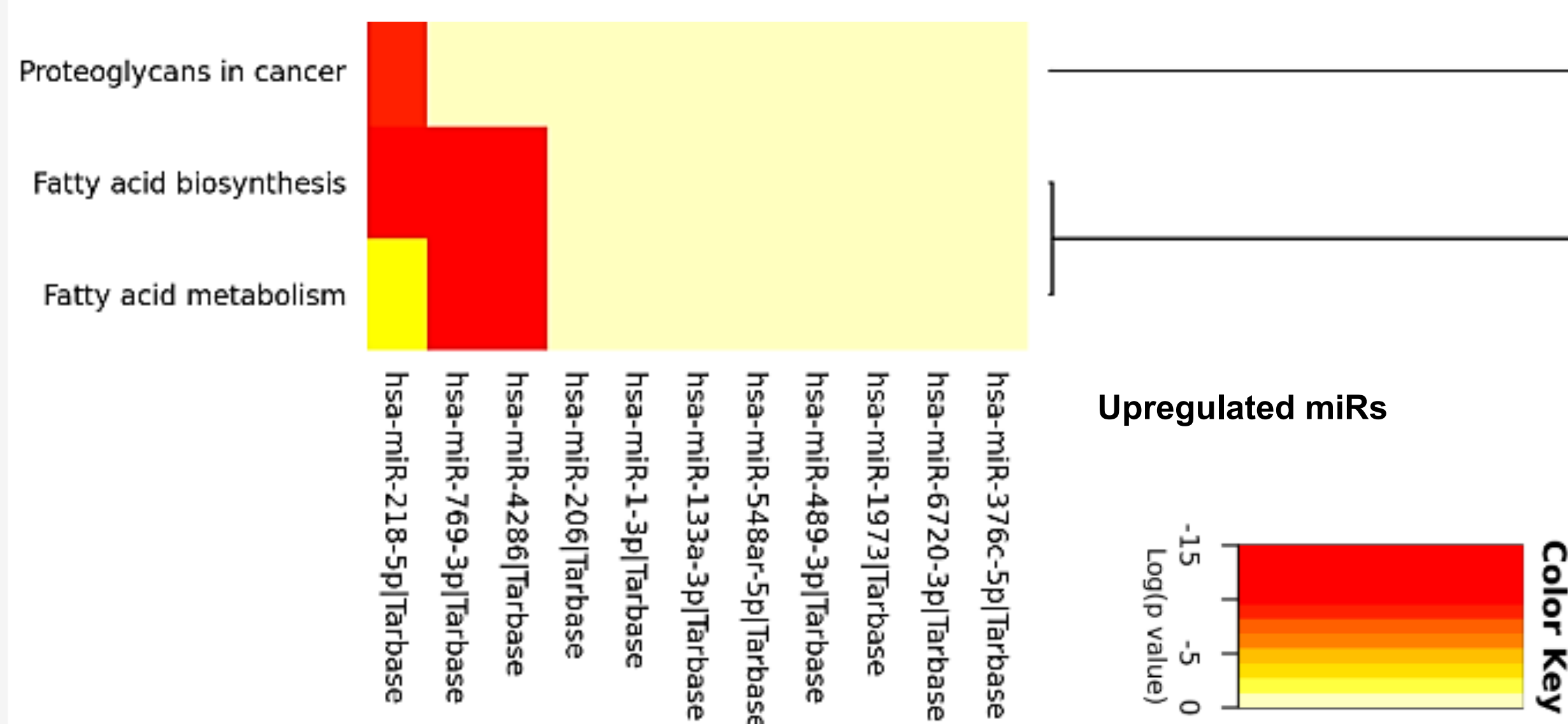
Differentially expressed miRs in ulcerated relative to non-ulcerated melanoma



Canonical pathways enriched by differentially expressed miRs in ulcerated melanoma



Downregulated miRs

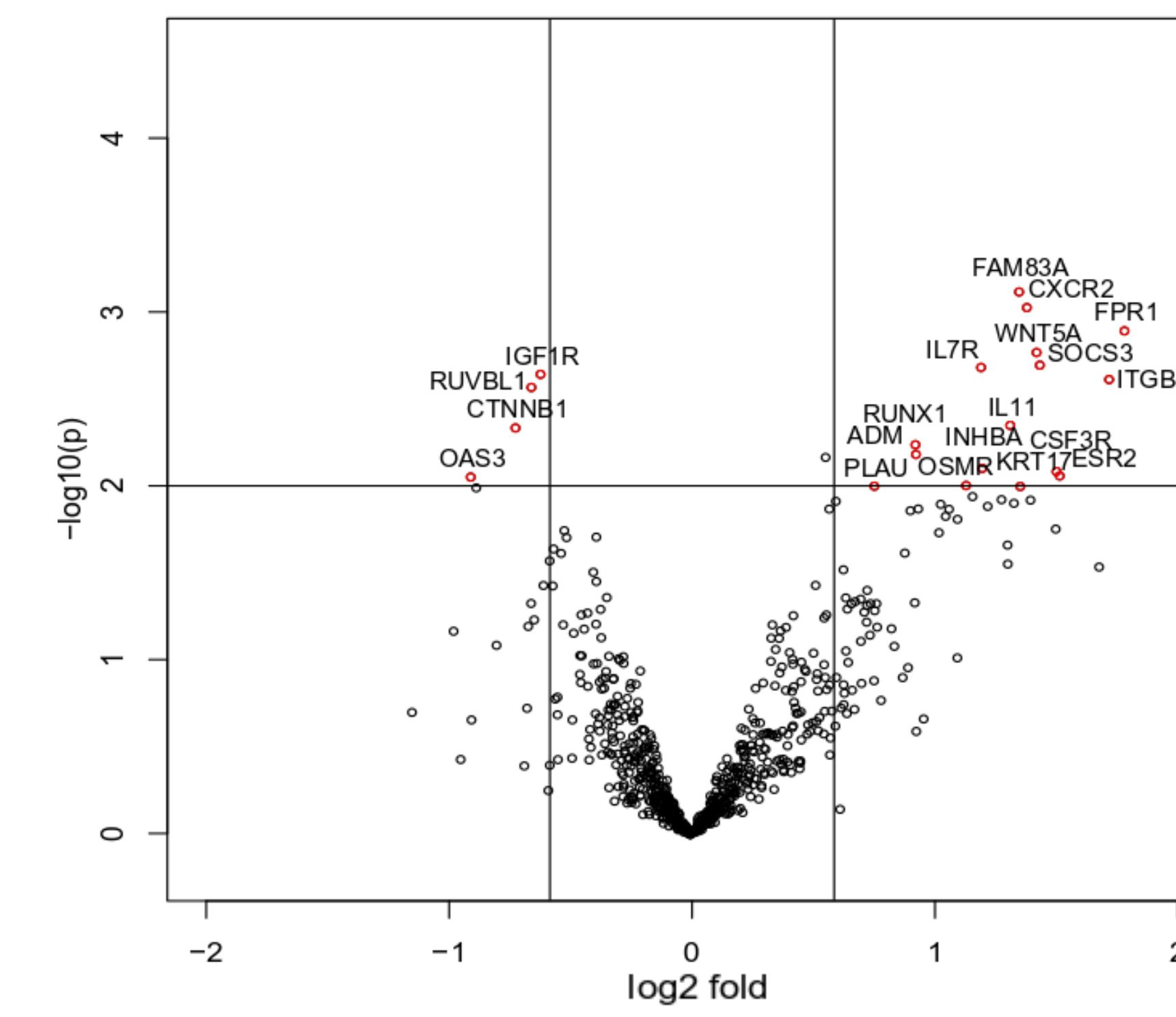


Upregulated miRs

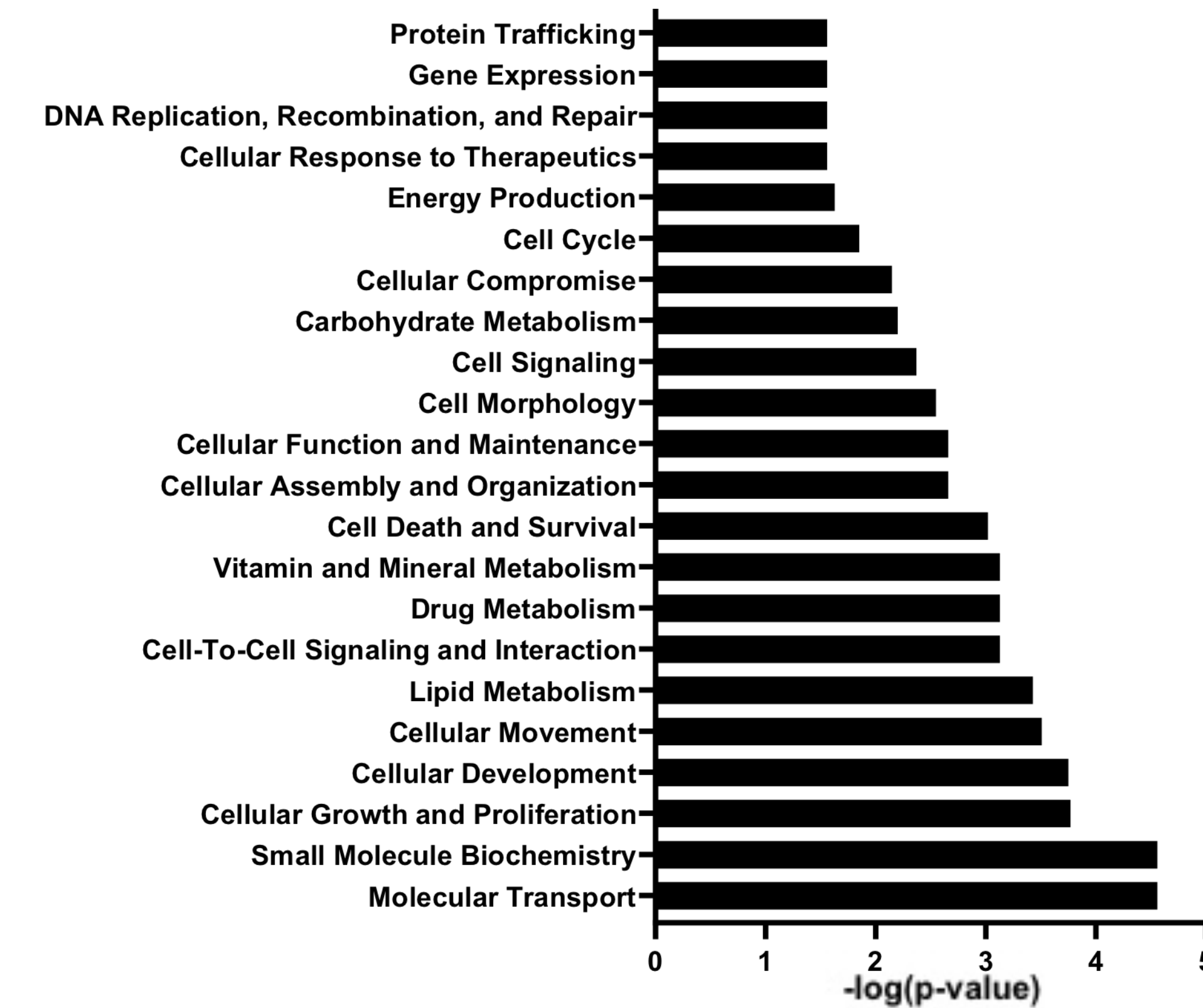


Results

Differentially expressed mRNA in ulcerated relative to non-ulcerated melanoma



Significantly enriched molecular/cellular functions based on differentially expressed mRNAs

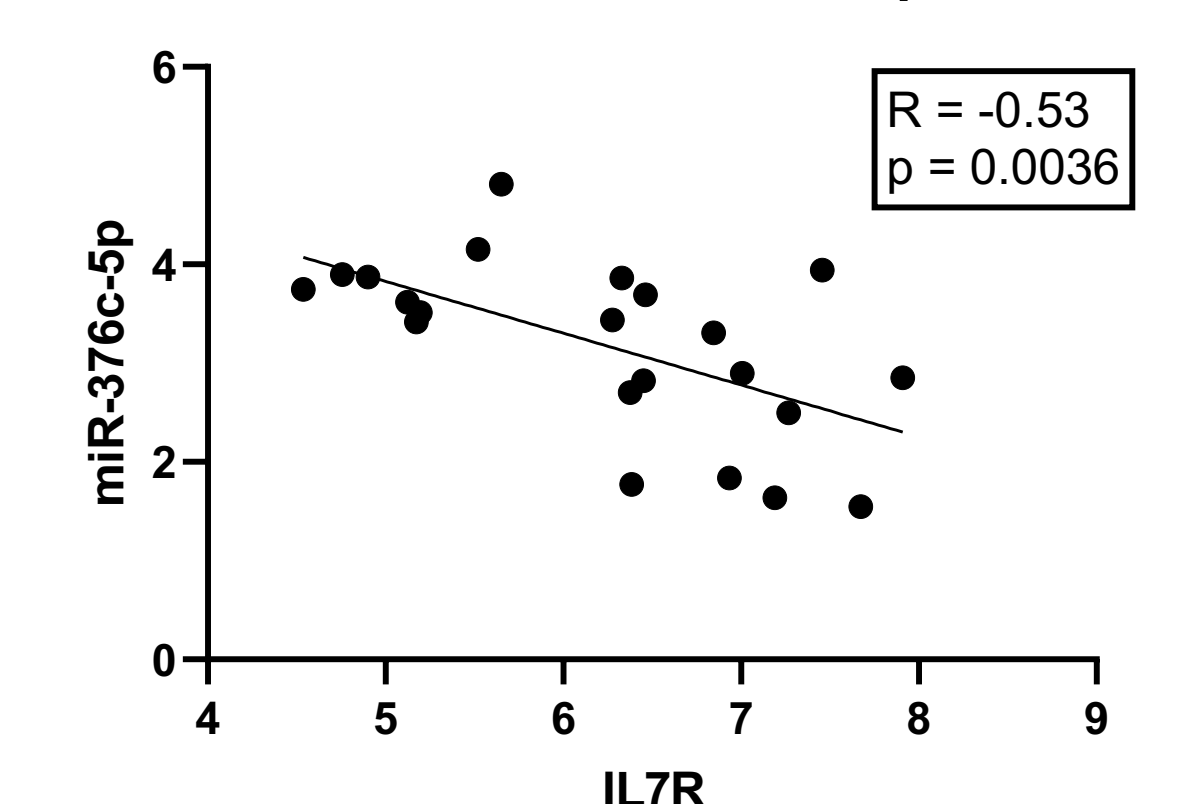
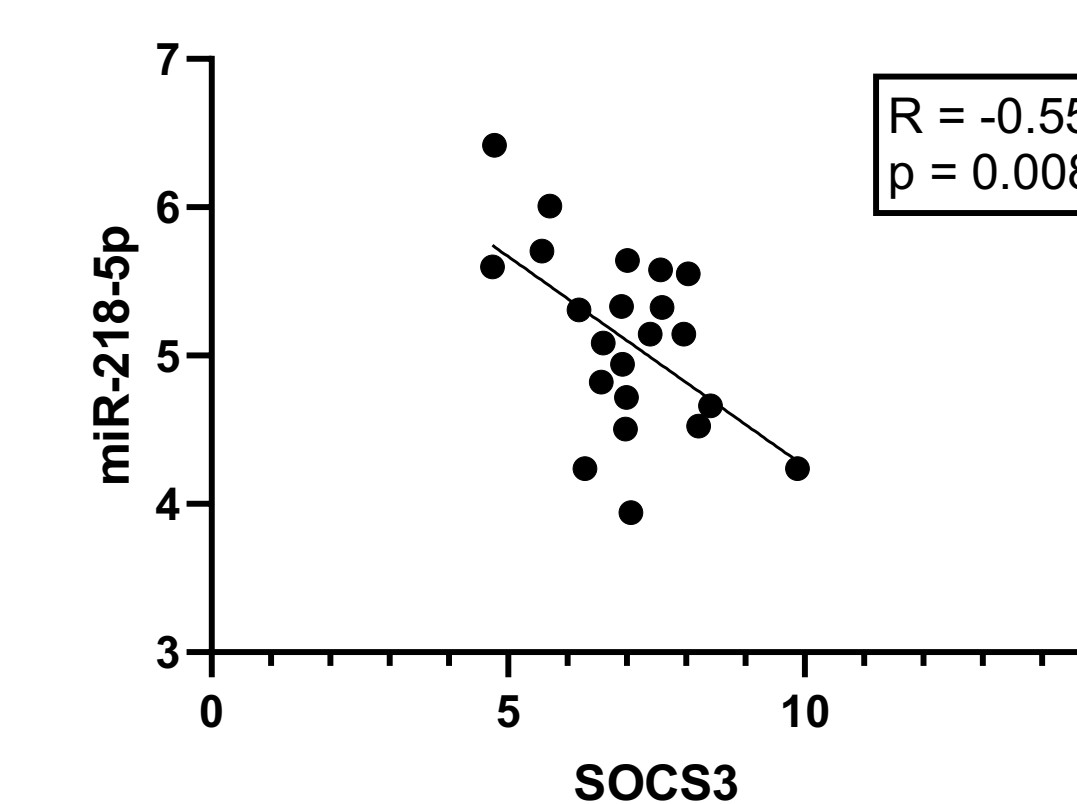
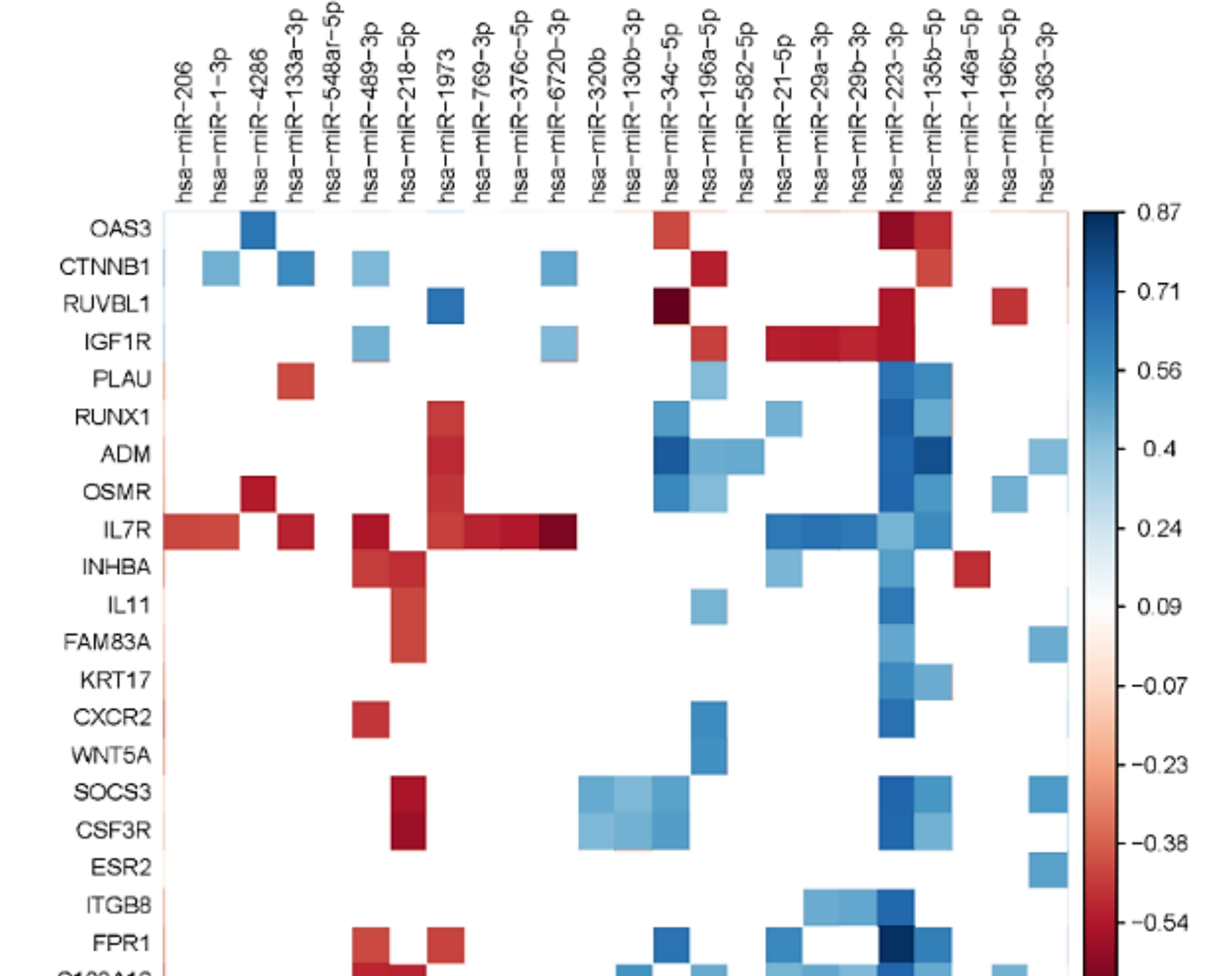


Differentially expressed mRNAs with predicted regulation by two or more differentially expressed miRs

Gene Name	Predicted Regulatory miRs
OAS3	miR-130b-3p, miR-135b-5p
CTNBN1	miR-21-5p, miR-29a-3p, miR-29b-3p, miR-320b, miR-363-3p, miR-582-5p
IGF1R	miR-21-5p, miR-196a-5p, miR-223-3p
RUNX1	miR-1-3p, miR-133a-3p
ADM	miR-1-3p, miR-133a-3p
OSMR	miR-1-3p, miR-133a-3p, miR-218-5p
INHBA	miR-1-3p, miR-218-5p
WNT5A	miR-1-3p, miR-218-5p, miR-769-3p
ITGB8	miR-1-3p, miR-133a-3p

Results

Pearson correlations of miR-mRNA pairs with inverse expression patterns



Conclusions

- A unique subset of miRs and mRNAs are differentially expressed in ulcerated melanoma relative to non-ulcerated
- Differentially expressed mRNAs in ulcerated melanoma are targets of multiple miRs with which they exhibit inverse correlations in expression
- Each upregulated mRNA in both the original and validation cohorts have been associated with angiogenesis, migration or pro-metastatic cell survival in cancer
- These findings provide novel insight regarding how increased angiogenesis and metastasis may contribute to melanoma tumor ulceration

Acknowledgements

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