Interferon Pathway Underexpressed in Melanoma Patients with Poor Prognosis

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Abstract

Predicting the prognosis of melanoma using current clinical approaches is very challenging and unreliable. Therefore, clinicians are seeking more accurate molecular markers to improve extant risk models.[4] Accordingly, we applied a methodology using three eigengenes to 404 samples from The Cancer Genome Atlas cohort of skin cutaneous melanoma.[2] Our survival analysis identified three groups of samples that have significantly different survival rates, with p-value < 10^{-5}. For instance, while about 60% of predicted low risk patients survived more than 6 years, only 5% of our predicted high-risk patients survived that long.

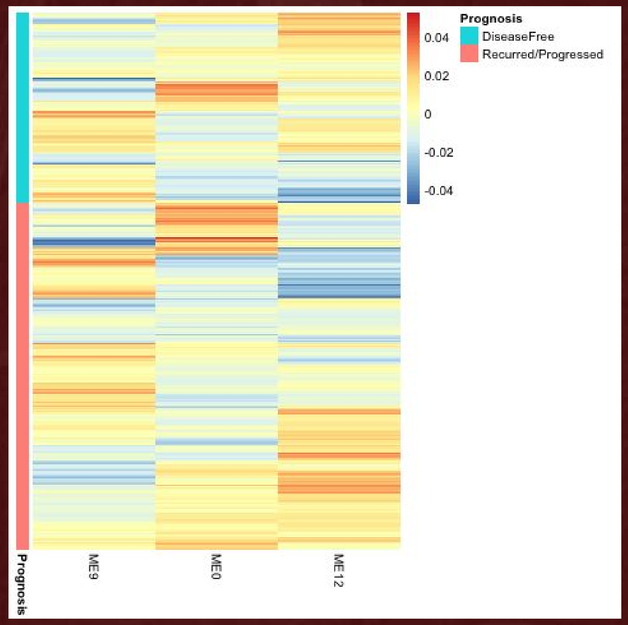


Fig. 1: A heatmap of eigengene expression in each patient for the mitotic cell cycle, interferon pathway, and outlier genes modules. Patients are grouped by status.

Citations

1. Cancer Genome Atlas Network. (2015). Genomic classification of cutaneous melanoma. *Cell*, *161*(7), 1681-1696.
2. Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. Cell. 2015 Jun 18; 161(7):1681-96.
3. Langfelder, P., & Horvath, S. (2008). WGCNA: an R package for weighted correlation network analysis. *BMC bioinformatics*, *9*(1), 1.
4. Grimm EA, Sikora AG, Ekmekcioglu S. Molecular pathways: inflammation-associated nitric-oxide production as a cancer-supporting redox mechanism and a potential therapeutic target. Clinical Cancer Research. 2013 Oct 15;19(20):5557-63.
5. Amir Foroushani et al.(2016) Large-scale gene network analysis reveals the significance of extracellular matrix pathway and homeobox genes in acute myeloid leukemia, Foroushani et al., In preparation. URL: http://oncinfo.org/.

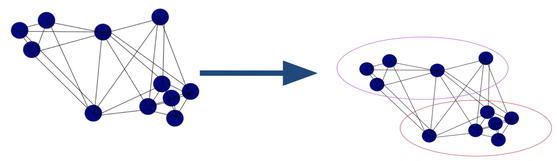
Methodology

Obtaining Data

We downloaded gene expression data as well as clinical data from 473 skin cutaneous melanoma patients from The Cancer Genome Atlas (TCGA).[1]

The Gene Network

We build a weighted gene correlation network using functions in the WGCNA R package.[3]



Each dot represents a gene. Each line is a connection (the correlation) between each gene.

The network is then clustered into gene modules.

Clustering and Eigengenes

- The R package Pigengene was used to perform clustering and eigengene computation.[5]
- The clustering yielded 13 clusters with 1404 outliers. An **eigengene** (first principle component of gene expression) was computed for each module.

Survival Analysis

A Penalized Cox Regression was performed to obtain the modules that best predict recurrence/progression.

The best three modules across many runs were:

- The outliers.
- A module associated with the mitotic cell cycle.
- A module associated with the interferon pathways.

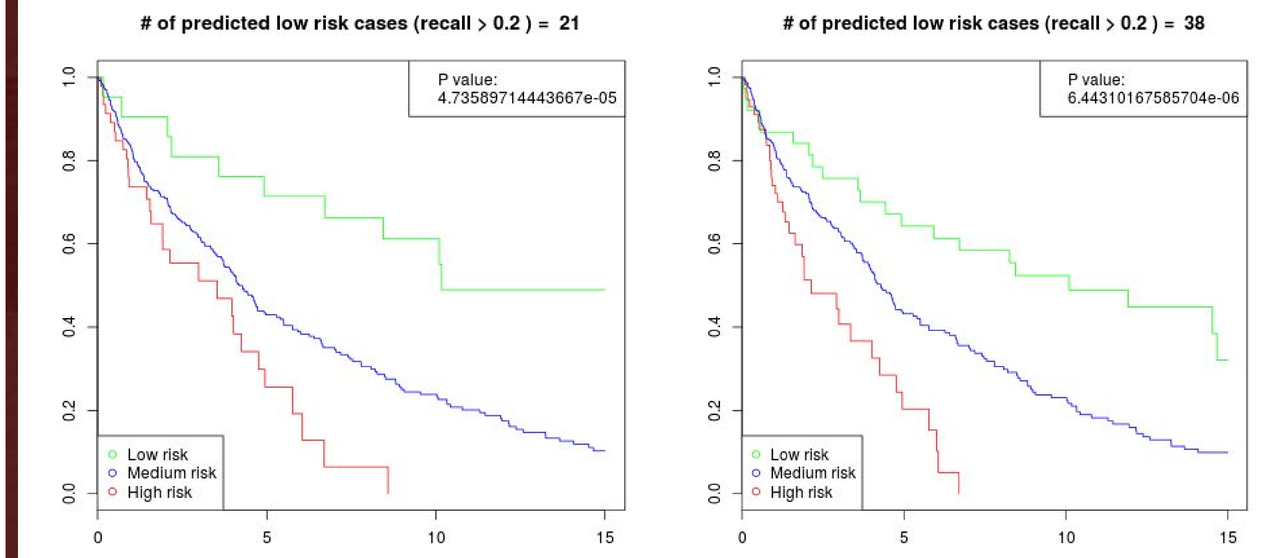


Fig. 2: Kaplan-Meier plots for survival probability of several risk groups using gene modules to predict survival probability (event of interest being recurrence/progression of melanoma). From left to right: (A) Plot using outliers and mitotic cell cycle. (B) Plot using outliers, mitotic cell cycle, and interferon pathways.

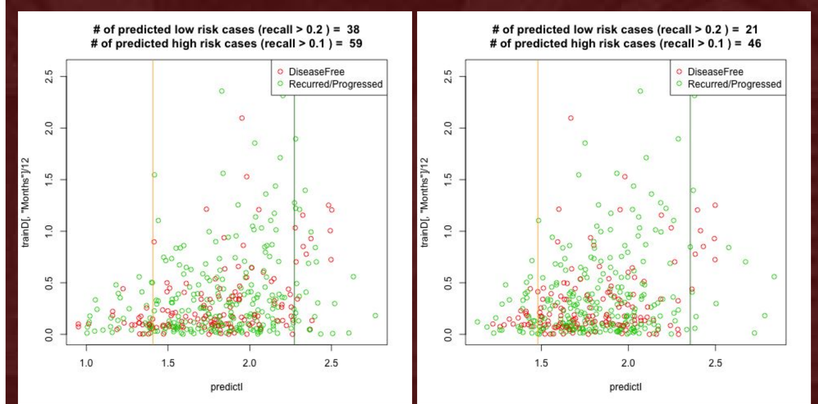


Fig. 3: Left to right:

(A) Plot of predictions for each patient using the mitotic cell cycle, interferon pathway, and outlier modules.

(B) Plot of predictions for each patient using the mitotic cell cycle and outlier modules.

Results and Conclusion

For the predictions in Fig. 2 (A), 21 patients were classified as low risk, while 46 were classified as high risk. For the predictions in Fig. (B) 38 were classified as low risk, while 59 were classified as high risk. Since more patients were classified in the low/high risk dichotomy in Fig. 2 (B), and the p-value was lower with similar survival predictions, we believe that the interferon pathway has a role in determining prognosis.

Other researchers should also use different methodologies to confirm whether the interferon pathway has a significant impact on the time of recurrence/prognosis or even time of death.

Acknowledgments

We thank the National Science Foundation for funding this research under the Research Experiences for Undergraduates Program, CNS-1358939, and NSF-CRI 1305302 awards.

We also thank Rupesh Agrahari for his supply of the template for this poster.