IMPACT OF GENE REGULATION IN THE CROSS-TALK BETWEEN THE IMMUNE SYSTEM AND MELANOMA TUMORS

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BACKGROUND

Cutaneous melanoma is the leading cause of death related to skin cancer. Most melanomas present an intense inflammatory infiltrate in the micro-environment along with several mechanisms of immune escape used by the tumor. Changes in the epigenetic and miRNAs expression profile are found in many types of cancer and can affect tumorigenesis through regulating tumor-associated stromal components including fibroblasts and immune cells. This project aims to evaluate the influence of miRNA and methylation alterations in the inflammatory profile of TCGA's metastatic melanoma samples and its correlation with clinical and pathological outcomes.

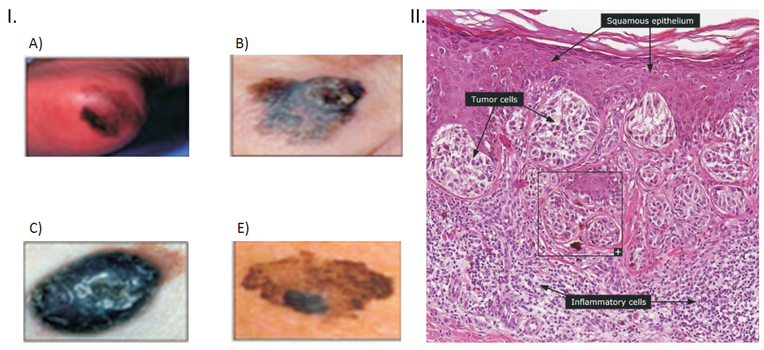
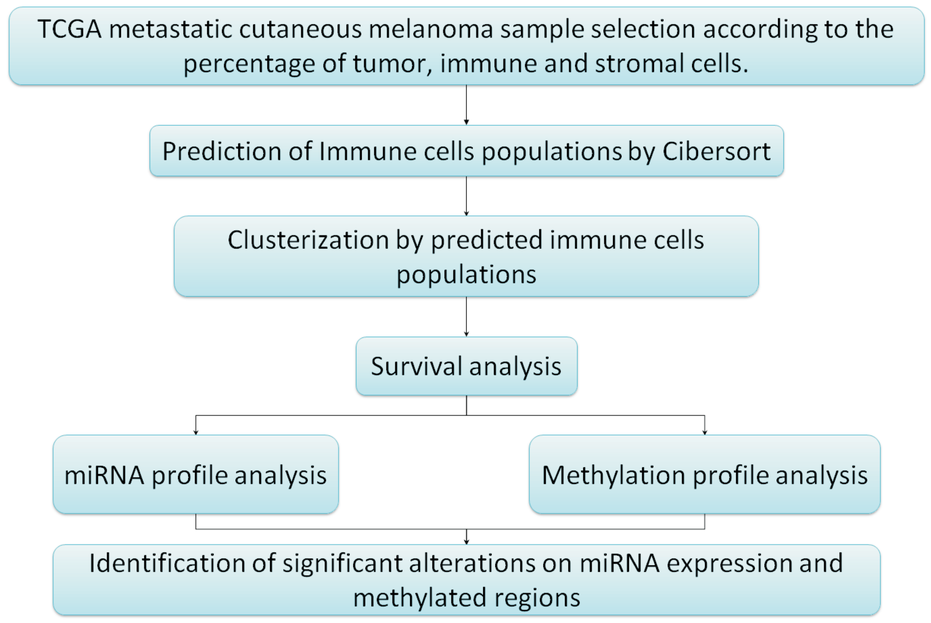


Figure 1. Melanoma. I. Major melanoma subtypes. A) Acral lentiginous. B) Lentigo Maligna. C) Nodular. D) Superficial Spreading. II. Superficial Spreading malignant melanoma hystological cut showing the melanoma tumors and adjacent inflammatory cells. Source: I. *US Pharm.* 2008;33(4)(Oncology suppl):31-35. II. The Human Protein Atlas (https://www.proteinatlas.org

MATERIAL AND METHODS



RESULTS AND DISCUSSION

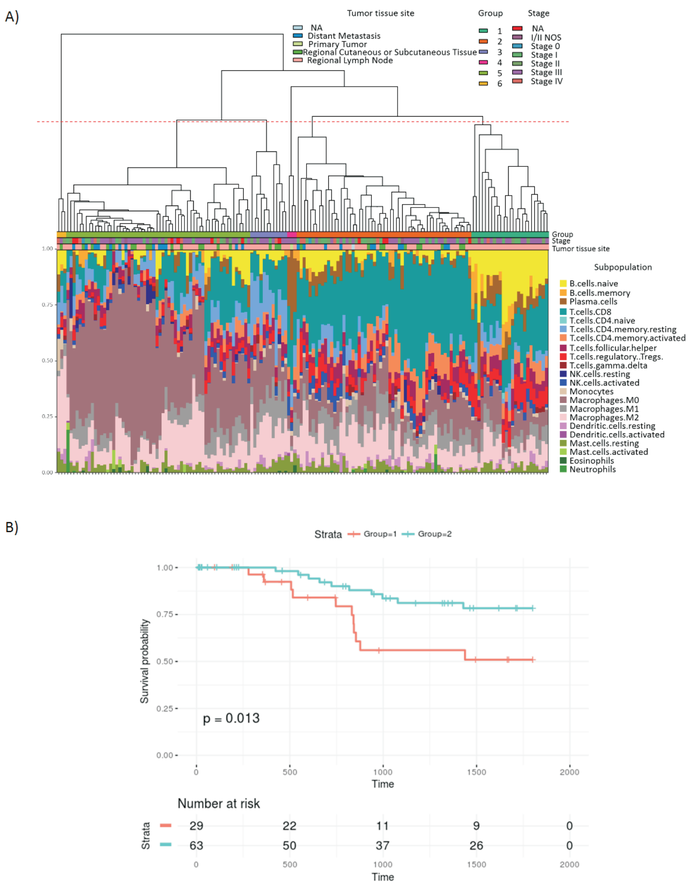


Figure 2. Prediction of Immune cells populations in the TCGA metastatic cutaneous melanoma samples. A) Hierarchical clustering according to the predicted immune cell populations by Cibersort. The red dotted line shows the height of the cut which separates the samples into 6 distinct groups. B) Kaplan Meyer survival curve between groups 1 and 2. The table below shows the number of living patient at every 500 days. C) Comparison of the percentage of the predicted immune cells populations between groups 1 (green) and 2 (orange).

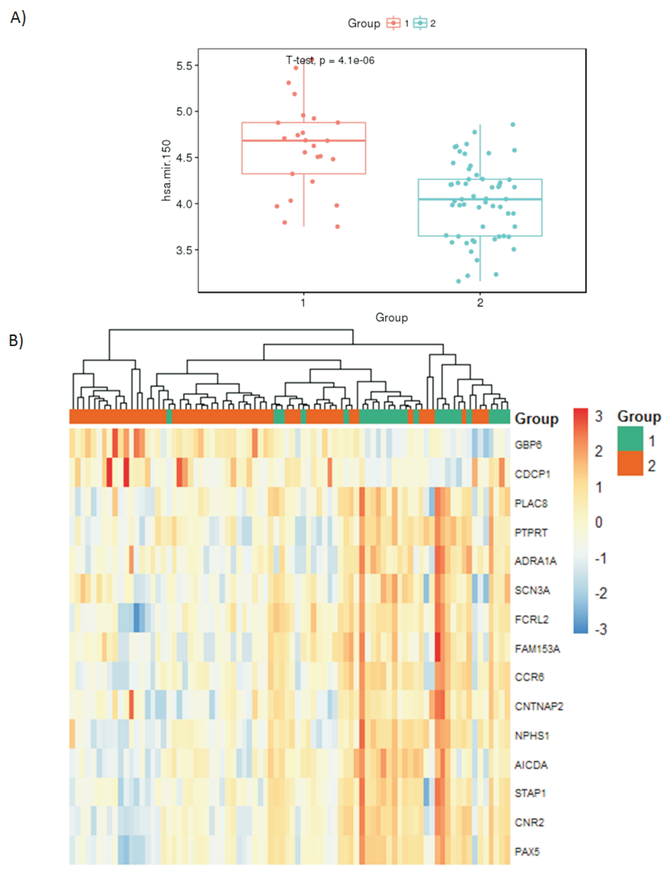


Figure 3. miRNA analysis. A) Comparison of hsa-mir-150 normalized expression estimates between groups 1 and 2. B) Heatmap of the normalized expression estimates of the hsa-mir-150 target genes that presented significant expression differences (adjusted p-value < 0.05) between groups 1 and 2.

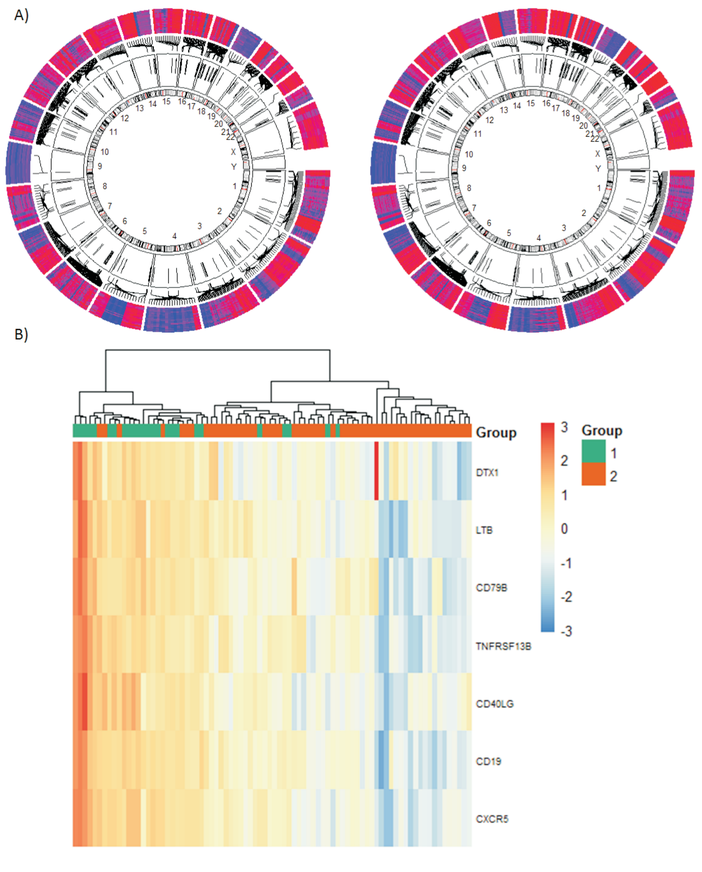


Figure 4. Methylation analysis. A) Circos plot of the differentially methylated regions (group 1 on the right and group 2 on the left). Red indicated hyper methylated regions and blue hypomethylated regions The inner circles indicate the chromosomal position of the differentially methylated region. B) Heatmap of the normalized estimates of the differentially expressed (adjusted p-value < 0.05) genes in the differentially methylated regions (adjusted p-value < 0.05) between groups 1 and 2.

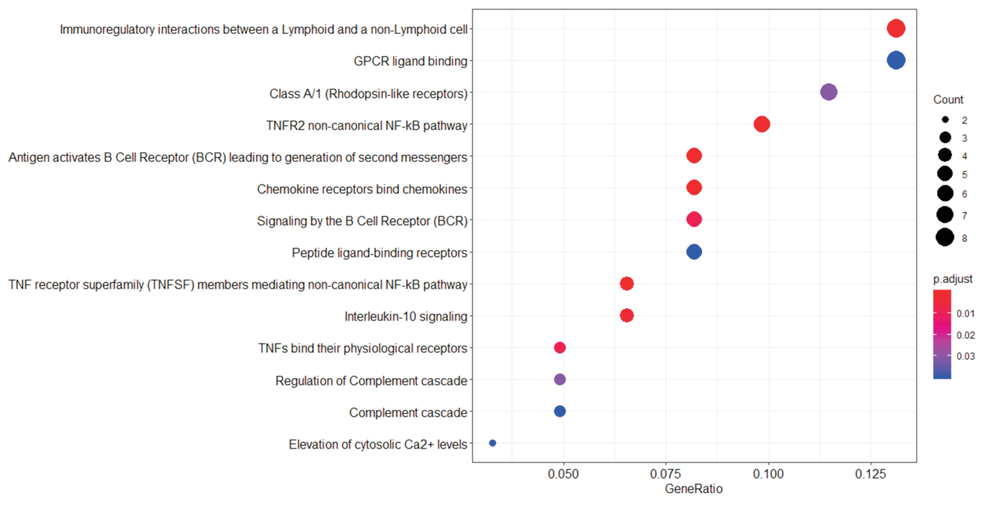


Figure 5. Enriched pathways of significant (adjusted p-value < 0.05) differentially expressed genes between groups 1 and 2 using ReactomePA. Circle size is proportional to the number of genes present in the pathways. The x axis represents the ratio between the number of genes found and the total of genes in the pathway.

CONCLUSION

The immune microenvironment in solid tumors can be determinant to disease progression and outcome. The analysis shows the impact of miRNA and epigenetic regulation of differentially expressed immune cell receptors between tumors associated with different stromal components. Genes involved in the regulation of cell growth, differentiation and proliferation, such as *PTPRT, ADRA1A, FCRL2*, potential miR-150 targets, as well as genes located in differentially methylated regions such as *CD79B, LTB* and *TNFRSF13B* are down regulated in the T cell-enriched group (Group 2), which shows better prognosis. The correlation between these levels of expression and the survival outcome still needs to be evaluated, but may reinforce the role of these gene expression regulation mechanisms in the melanoma microenvironment. The characterization of the different immune infiltrate profiles that discriminate melanoma into distinct subgroups can contribute to the understanding of the role of microenvironmental factors in melanoma progression and to the identification of prognostic biomarkers.

Projeto Gráfico: Setor de Edição e Informação Técnico-Científica / INCA