Bioinformatics insights in etiopathogenesis, diagnosis and therapy of Cutaneous T-cell lymphoma

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Introduction

The pathogenesis of Cutaneous T-cell lymphoma (CTCL) remains poorly understood and the early diagnosis of CTCL is difficult. The histologic diagnosis of early MF is one of the most vexing problems in dermatopathology [1,2]. **Importantly, several significant and/or benign conditions such as atopic dermatitis and psoriasis may mimic MF histologically and result in misdiagnosis** [2]**.**

Although many studies have focused on the understanding of the molecular mechanisms underlying CTCL, the field is still unclear and under elucidation. **Bioinformatics can give extra insights in the etiopathogenesis, diagnosis and possible therapy of the disease through omics analytics and pathway analysis.**

Our aim was to apply state-of-the-art bioinformatic tools in order to unravel the mechanisms of MF pathobiology, to address new therapeutic possibilities as well as to identify potential biomarkers.

Materials & Methods

Bioinformatic tools and database were used in a multitask project targeting at differentially expressed genes in MF, implicated pathways involved in the development of MF as well as in the differential expression of miRNAs (miRs).

1. **Datasets Selection**: we searched the GEO (http://www.ncbi.nlm.nih.gov/geo/) for gene (GSE143382) [3] and miRNA (GSE109421) [4] expression datasets containing early-stage MF samples and reactive skin lesions (inflammatory dermatosis) as control.
2. **Differential expression data analysis:** was performed in R programming language using the LIMMA R package [5]. Differentially expressed genes (DEGs) were selected by applying selection thresholds of adjusted p-value < 0.05 and absolute (log2FC) >= 1 (i.e. FC>=2 or FC<=0.5). For the case of differentially expressed miRNAs (DEMs) we used as selection criteria the p-value < 0.05 and the FC≥1.2 for the over expressed miRNAs and FC≤0.83 for the under expressed ones. Focusing more on the over-expressed miRNAs, we further filtered out by keeping the ones with strong experimentally validated interactions with genes known to be implicated in CTCL, using miRTargetLink [6] which offers detailed information on human microRNA-mRNA interactions.
3. **Pathway Enrichment Analysis using DEGs**: was performed using the Enrichr, a web-based tool for analysing gene sets that returns any enrichment of common annotated biological features (https://maayanlab.cloud/Enrichr/) [7] .
4. **Pathway Enrichment Analysis using DEMs**: was performed using the DIANA-mirPath [8] which is a miRNA pathway analysis web-server, which can utilize experimentally validated miRNA interactions derived from DIANA-TarBase v6.0.

The enrichment was obtained using information from KEGG Human and the most significantly enriched pathways were selected based on the p-value <0.05.

Conclusion

- Bioinformatics were used as a stepping-stone in a combined approach highlighting **differentially expressed genes** and **miRNAs** as well as the implicated **pathways** involved in MF development.
- These findings formed a resource of genes and miRNAs that will be further tested in vitro and in vivo in order to identify the **etiopathogenesis** of the disease, discover **biomarkers** for diagnosis and highlight **new therapeutic targets**.

References

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Results

Our bioinformatics analysis detected:

1. **A list of DEGs in MF** which are associated with increased cell proliferation, decreased apoptosis, increased Th2 differentiation and immune activation leading to generation of malignant CD4+ T-cells clones, propagating the disease.

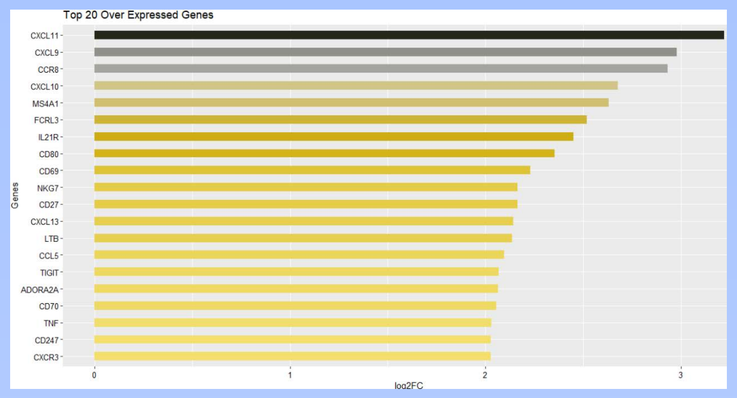

***Figure 1**:Top 20 Over Expressed Genes*

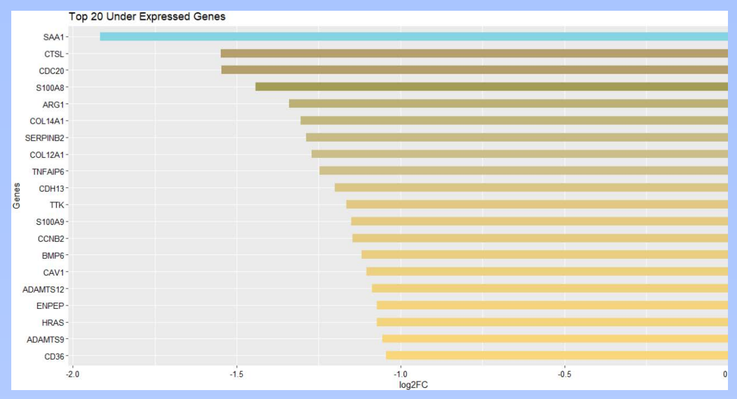

***Figure 2**:Top 20 Under Expressed Genes*

2. **A list of DEMs in MF.** A more restricted set of overexpressed miRNAs (miR-26a, miR-92a, miR-106b, miR-142, miR-146a, miR-155, miR-181a, miR-222 and miR-494) were selected using miRTargetLink and could be therefore used as biomarkers. The aforementioned miRs present strong experimentally validated interactions with genes in crucial signaling pathways for CTCL pathogenesis (MAPK/ERK, PI3K/AKT and especially in JAK/STAT pathway).

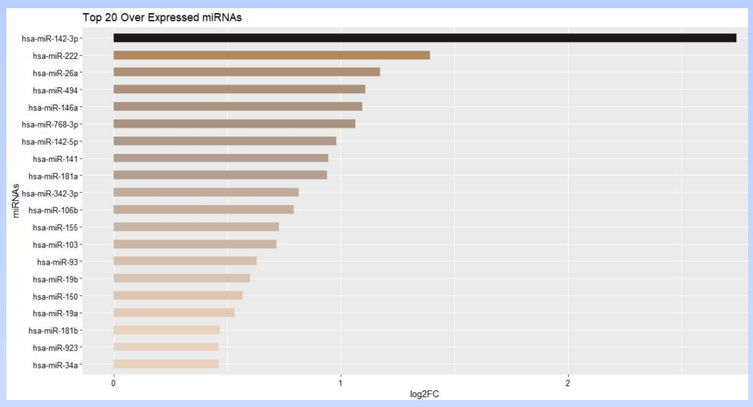

***Figure 3**:Top 20 Over Expressed miRNAs*

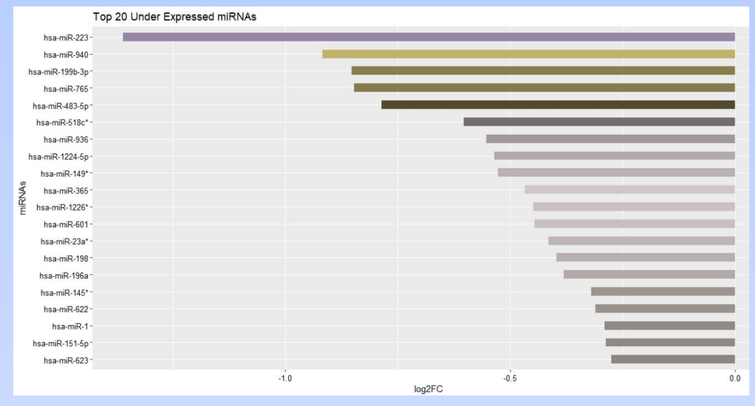

***Figure 4**:Top 20 Under Expressed miRNAs*

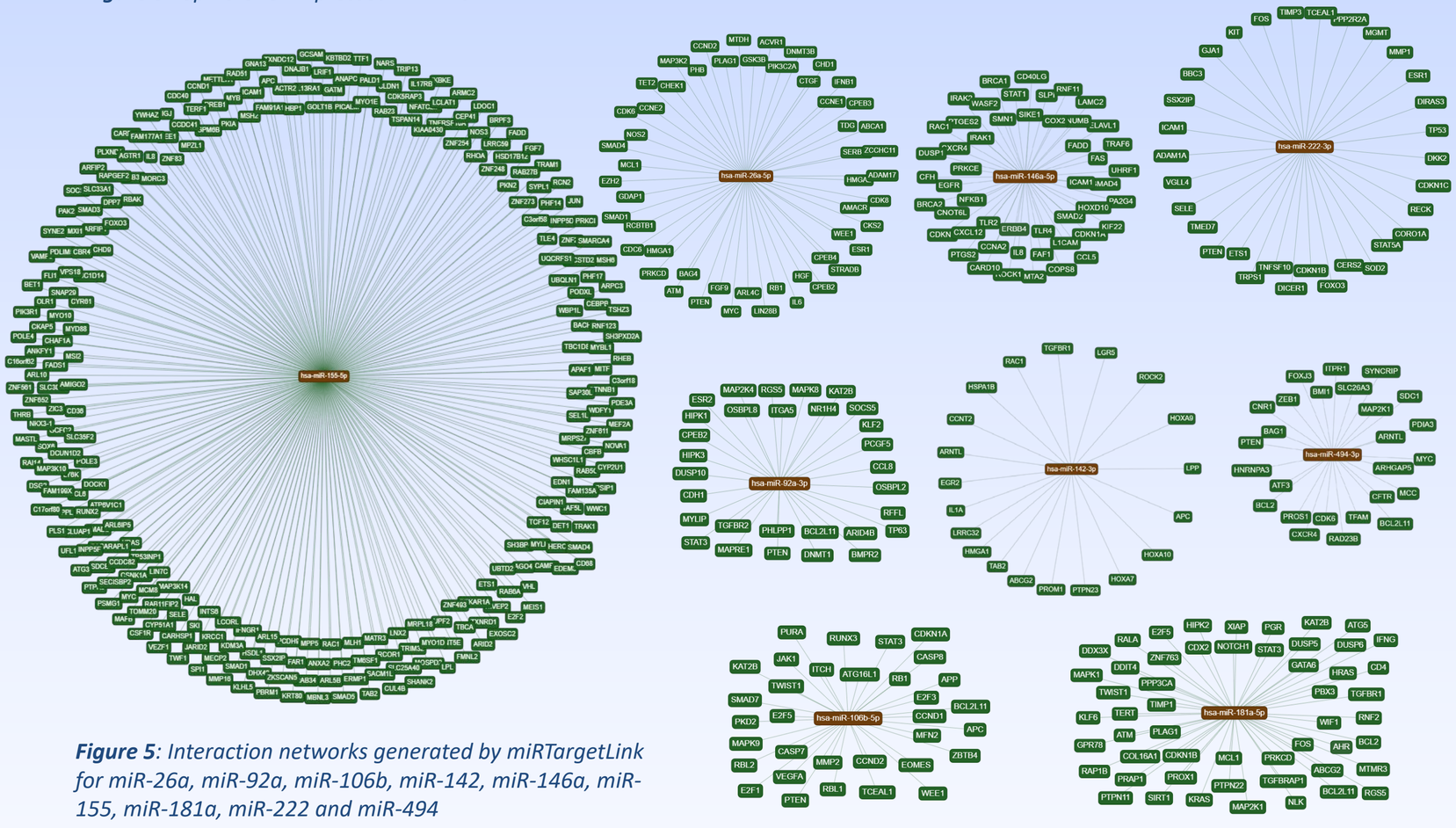

***Figure 5**: Interaction networks generated by miRTargetLink for miR-26a, miR-92a, miR-106b, miR-142, miR-146a, miR-155, miR-181a, miR-222 and miR-494*

3. **A number of pathways** that have been extracted from the genes and miRNAs implicated in pathogenesis of MF and can enlighten its etiopathogenesis. Fourteen percent (14%) of the pathways were common in both analyses.

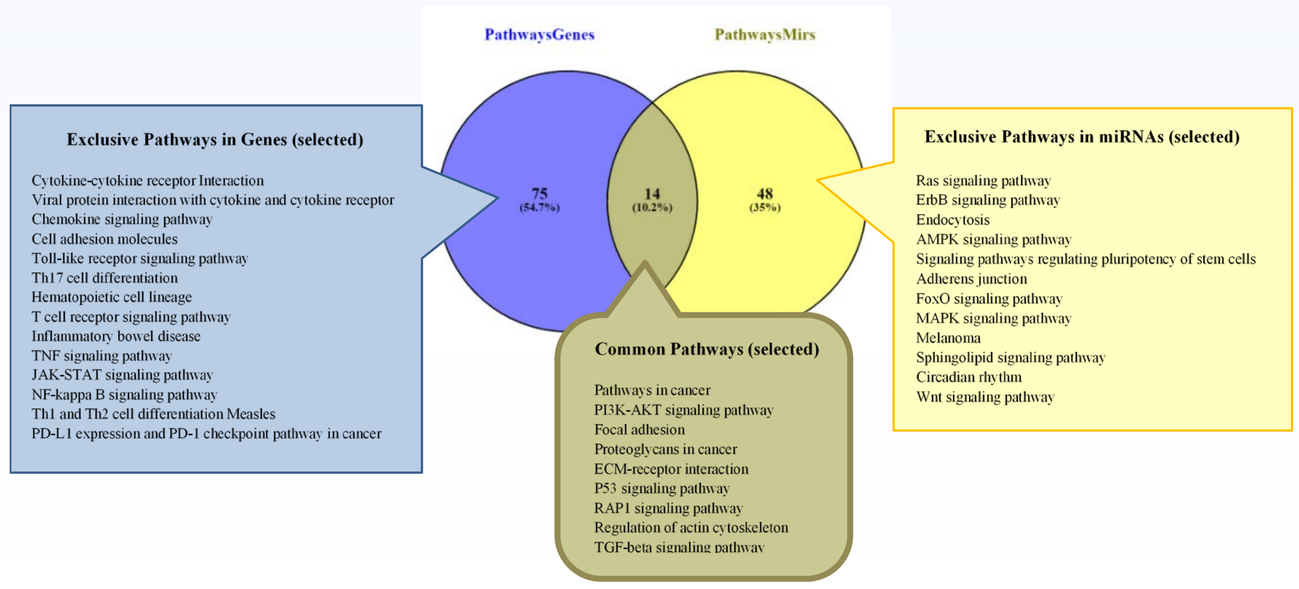

***Figure 6**: Selected pathways extracted from the genes and miRNAs implicated in pathogenesis of CTCL*