Differentially Expressed miRNAs and mRNAs in Psoriatic Skin

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Background

Psoriasis is a chronic immune-mediated skin disease with an estimated global prevalence of 1-3%. Interestingly, several studies have reported a substantially higher prevalence in Norway, ranging from 5.8% to 11.4% (1, 2).

For the past seven decades, the influence of genetics in the development of psoriasis has been recognized (3). Since then, genome-wide association studies have identified >60 loci associated with the disease.

Much of our knowledge of the molecular contributors of the disease has come from transcriptional studies of psoriatic skin samples, which have identified several dysregulated messenger RNAs (mRNAs) and microRNAs (miRNAs) in psoriasis (4, 5). miRNAs are short, non-coding RNAs which have the ability to regulate gene expression on a post-transcriptional level, through silencing or repression of mRNAs (6). However, for most studies, the sample sizes have been relatively small and no large-scale transcriptomic study has been conducted on Norwegian skin samples.

To increase our understanding of the pathophysiology of psoriasis we aimed to do in-depth investigations on the psoriasis transcriptome using samples from our recently established biobank.

Materials and Methods

We collected skin biopsies from lesional (PP) and non-lesional (PN) skin of psoriatic patients (n = 75) and controls (NN) (n = 46). The biopsies were snap-frozen in liquid nitrogen and sequenced on Illumina HiSeq4000 flow cells.

Differential expression analysis was performed using *limma*, comparing PP to NN, PP to PN and PN to NN. We predicted the targets of the dysregulated miRNA using miRBase. We performed gene ontology (GO) analysis on the dysregulated mRNA and the predicted targets of the dysregulated miRNAs, as well as functional clustering analysis using *DAVID* v6.8 for the genes with a $|\log_2 FC| \geq 2$.

Discussion and Conclusion

Our results support a model for psoriasis as a result of perturbed interaction between keratinocytes and activated immune cells, leading to an increased proliferation rate of keratinocytes and epidermal thickening. Both the number of differentially expressed genes and functional enrichment of mRNAs are concordant with both the clinical presentation and previous studies of psoriasis.

We aim for further systematic analysis using network tools and to identify pairs of miRNA and mRNA with anti-correlated expression patterns. By combining blood expression quantitative trait loci (eQTLs) and tissue expression, we will determine to what extent disease-associated genetic variants and expression differences between psoriasis-related and normal skin are reflected in blood composition or gene expression.

Results

mRNA:
We identified a total of 14,242 significantly differentially expressed genes (DEGs) across all contrasts. There was a substantial overlap between the contrasts as shown in Figure 1.

When comparing PP to NN we identified 11,297 DEGs. When comparing PN to NN, we identified 50 DEGs. Functional enrichment clustering of the DEGs in the PP/NN contrast identified 'immunity', 'keratinization' and 'cell division' for the up-regulated genes. The down-regulated genes showed enrichment for 'glycoprotein/cell membrane', 'disulphide bond' and 'cell adhesion'.

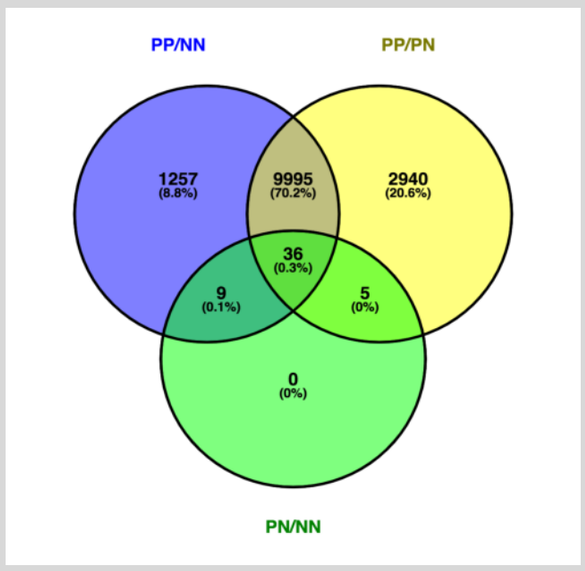

Figure 1. Venn-diagram of overlapping DEGs between the different contrasts.

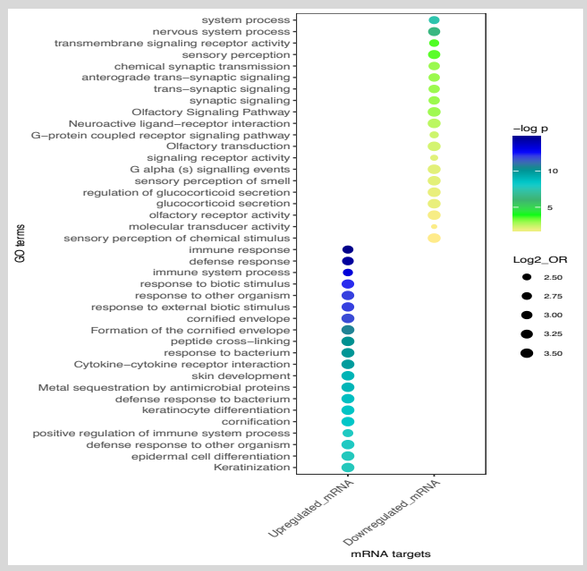

Figure 2. Enrichment of GO terms for DEGs for PP/NN.

miRNA:
We identified a total of 543 differentially expressed miRNAs. They also showed substantial overlap between the comparisons, with 424 miRNA (78.1%) being shared between the PP/NN and PP/NN contrast (Fig 3). No miRNA reached significance when comparing PN to NN skin. Of the 543 differentially expressed miRNAs identified, 220 were novel for psoriasis.

Gene ontology analysis of the predicted targets of the significantly differentially expressed miRNAs, displayed enrichment for various signaling pathways and cancer terms. As the enriched terms were quite broad, there was a substantial overlap between the GO results of the targets of the up-regulated and down-regulated miRNAs as shown in Figure 4.

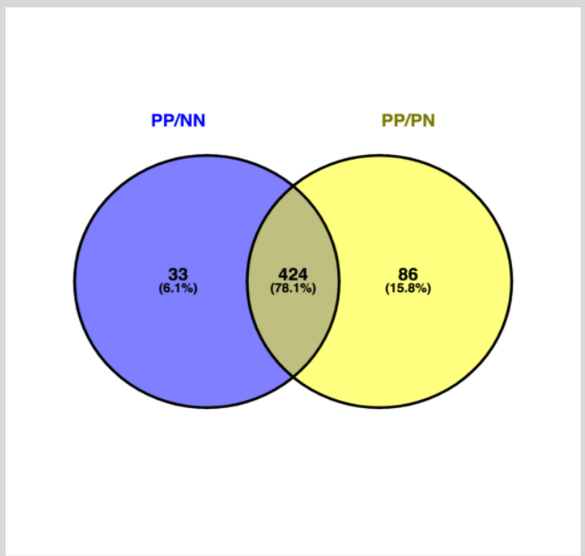

Figure 3. Venn-diagram of overlapping differentially expressed miRNA transcripts between the different contrasts.

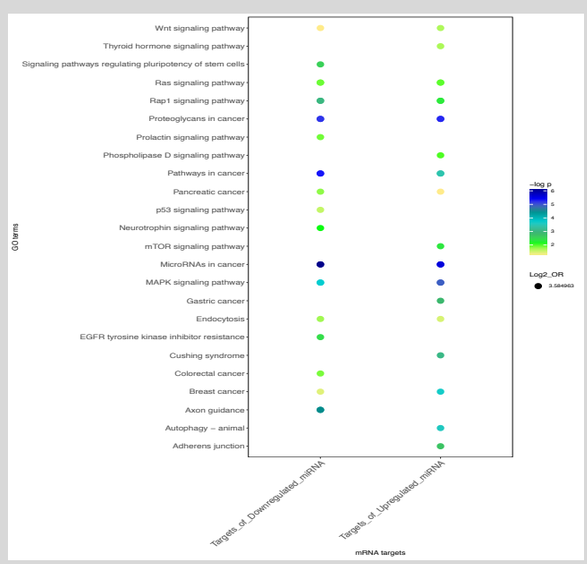

Figure 4. Enrichment of GO terms for the predicted targets of up- and downregulated miRNA in the PP/NN contrast.

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