LIVERPOOL JOHN MOORES UNIVERSITY

MicroRNA expression and Function in Lichen Planopilaris

Cicatricial Alopecia Research Foundation

Grant Report 2022

DR KEHINDE ROSS

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Lay Summary

Complex diseases are underpinned by defective control of genes and cell behaviour. These genes include *microRNAs* (miRNA), which fine-tune the biomolecular trajectories of cells by modulating biological pathways. However, the roles of miRNAs in scarring alopecia disorders such as lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA) have received limited attention.

Remarkable advances in genomic technologies have enabled us to uncover changes across hundreds of genes at a time. Using one such technique, we set out to find whether miRNA levels were altered in scalp skin samples from patients with LPP and FFA in order to establish their potential as targets for next generation RNA-directed therapeutics.

What did we find?

- The levels of 15 miRNAs appeared to be altered in LPP lesions compared to uninvolved scalp skin.
- Of these 15 miRNAs, the expression of 9 miRNAs appeared to be elevated while the levels of 6 were downregulated.
- Changes in the levels of miRNA in LPP lesions appeared minimal compared to FFA where almost 50 miRNAs were altered.
- Two of the miRNAs upregulated in LPP may inflammatory axes in LPP.

Altogether, our findings indicate that miRNA dysregulation may contribute to biological changes associated with LPP. However, further work is needed using larger patient cohorts to verify these observations. In addition, detailed molecular characterisation of the miRNA-targeted pathways associated with LPP is required, especially to support the development of miRNA therapeutics. Such work will help ensure that RNA-based technologies that have recently entered the clinic for a variety of rare diseases can be pivoted to tackle scarring alopecia.

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MicroRNA expression and Function in Lichen Planopilaris

Background

MicroRNAs (miRNAs) are now well-established as crucial regulators of diverse physiological and pathological processes. However, despite the early discovery of specific miRNAs in hair follicles, little is known about their roles in the scarring cicatricial alopecias. Several miRNAs are known to modulate inflammatory processes in the skin and other organs, but the putative roles of miRNA in lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA) have not been established.

Methods

Lesional and non-lesional scalp skin samples were provided by Dr Matthew Harries (Salford Royal NHS Foundation Trust, northwest regional ethics committee approval (reference 14/NW/0342). Total RNA was extracted and subjected to RNA sequencing Samples were Therefore we profiled the expression of miRNA in LPP and FFA samples using RNA sequencing at the Centre for genomics Research, University of Liverpool.

Key Findings

We identified 15 miRNAs in the LPP samples whose expression was dysregulated in LPP lesions compared to non-lesional samples, of which 9 miRNAs were elevated while 5 were downregulated. This contrasts with FFA, where changes in miRNA expression appeared to be more extensive, with 49 dysregulated miRNAs. The elevated miRNAs in the LPP samples included miR-21-3p and miR-223-3p, both of which have been implicated in inflammatory processes.

To gain insight into potential dysregulation of messenger RNA by these miRNAs, we performed global transcriptome analysis of the same LPP samples. We identified 32 genes that appeared to be elevated in lesional *versus* non-lesional samples. These included genes associated with inflammatory processes and epithelial-mesenchymal transition. However, no relationships were immediately apparent between the dysregulated genes and dysregulated miRNAs, at least based on bioinformatics predictions.

Conclusion

Taken together, our findings suggest that the expression of several miRNAs and mRNAs may be dysregulated in LPP. These findings have not been published yet but are supporting an application for further funding to develop microRNA-directed therapeutics for a range of diseases, including scarring alopecias. These are exciting times for RNA-based clinical interventions, as evidenced by the mRNA vaccines for COVID-19 and the regulatory approval of several short-interfering RNA (siRNA) drugs to treat rare disorders.