

Allergic Contact Dermatitis to Nickel Is Characterized by a Specific Micro-RNA Signature

To the Editor:

Allergic contact dermatitis (ACD) is a type IV delayed type hypersensitivity response to allergens that come in contact with the skin.¹ Micro RNAs (miRNAs) are noncoding RNA molecules that modulate gene expression post-transcriptionally.² Here, we investigated the miRNA expression in skin after challenge to nickel (Ni). Using global miRNA expression analysis on skin obtained from the challenge reaction (Ni and vehicle) from 3 subjects with a patch test positive to Ni (PP) and 3 healthy subjects with no history of dermatitis (NN) (Table S1, <http://links.lww.com/DER/A4>), we identified 159 miRNAs that were differentially expressed ($P < 0.05$; Table S2, <http://links.lww.com/DER/A4>). Unsupervised hierarchical clustering based on the 159 deregulated miRNAs showed a clear separation related to the elicitation reaction (Fig. 1A). Micro RNA-193a-3p was the only miRNA that was previously reported as deregulated in another allergen-induced ACD (diphenylcyclopropenone (DPCP)-challenged skin)³ indicating that the miRNA expression profiles in ACD may be allergen specific.

In an ACD reaction, immune cells migrate from the blood into the skin. To determine whether the disease-related miRNAs could be confined specifically to the immune cells in the dermal inflammatory compartment, we next investigated the global miRNA expression in peripheral blood mononuclear cells (PBMCs) exposed to Ni or vehicle. We found 19 miRNAs that were differentially expressed between PBMCs from subjects with allergy to Ni stimulated with Ni compared with vehicle ($P < 0.05$; Table S3, <http://links.lww.com/DER/A4>). Among those, miR-155 that previously has been shown to be increased in the dermal infiltrating immune cells in lesions from patients with psoriasis and atopic dermatitis,^{4,5} altogether suggesting a common inflammatory role of miR-155 in skin

diseases. A comparison between deregulated miRNAs in Ni-challenged skin and PBMCs from subjects with allergy to Ni showed only a minimal overlap (Fig. 1B). An explanation for the limited overlap could be the fact that the identified miRNA signature from the PBMCs may represent a systemic component rather than local miRNA changes in the skin. Finally, our sample population was small, and the adjusted P values were high increasing the risk of detecting false-positive miRNAs. Nonetheless, unsupervised hierarchical clustering of the PP skin samples and the PBMCs support that the changes in the miRNA expressions are related to biological variation.

Because ACD clinically can resemble irritant contact dermatitis (ICD), we finally sought to investigate whether miRNA expression profiles can be used to distinguish ACD

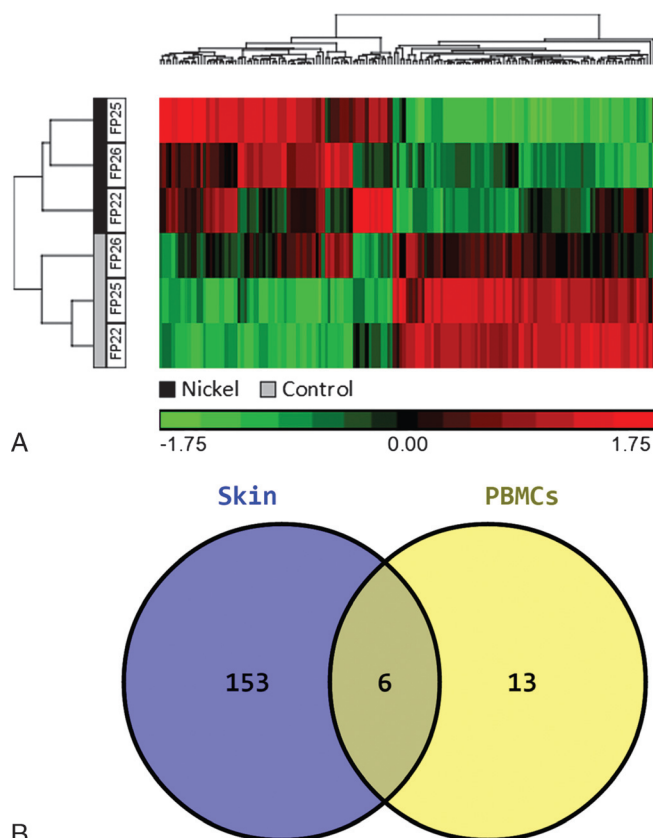


FIGURE 1. A and B, Micro RNA signature in Ni-challenged skin. A, Heat map illustrating levels of significantly deregulated miRNAs ($P < 0.05$) identified in skin from Ni-challenged skin (PP_{Ni}, black) compared with vehicle-challenged skin (PP_{vehicle}, gray). Samples are clustered both in rows (samples) and columns (miRNAs). Color intensity is scaled within each column so that the highest expression value corresponds to bright red and the lowest to bright green. B, Venn diagram showing the overlap of significantly upregulated miRNAs ($P < 0.05$) in (blue) skin from subjects with allergy to Ni (Ni vs vehicle-challenged skin) and (yellow) PBMCs from subjects with allergy to Ni (Ni vs vehicle-stimulated PBMCs).

Supported by the Danish Foundation for Advanced Technology (Højteknologifonden).

M.A.R. is employed by LEO Pharma A/S. L.S. received consultancy and/or speaker honoraria from Abbott, Pfizer, Janssen-Cilag, MSD, and LEO Pharma A/S and is a member of the Advisory Board of MDS, Novartis, Abbvie, and Janssen-Cilag. Furthermore, grants for research projects are received from LEO Pharma A/S, Pfizer, and Abbvie. M.B.L., B.D.A., A.C., M.T.V., and C.M.B. declare no conflict of interests.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.dermatitisjournal.com).

DOI: 10.1097/DER.000000000000127

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from ICD. We found 8 miRNAs that were significantly upregulated in healthy skin exposed to the irritant nonanoic acid ($P < 0.05$; Table S4, <http://links.lww.com/DER/A4>). A comparison of the miRNA expression signatures between Ni-induced ACD and nonanoic acid-induced ICD showed a limited overlap of deregulated miRNAs (miR-3182, miR-3613-3p, miR-4657). Although a direct comparison cannot be made because of the different time point used, these preliminary data may indicate that miRNA expression profiles can be used to distinguish ACD from ICD.

In summary, this is the first study to investigate the global miRNA expression in Ni-challenged skin from sensitized subjects. Our findings demonstrate that Ni-challenged skin in ACD is characterized by a specific miRNA signature. Because of the low number of subjects included, this study should be considered as exploratory only. Further studies are warranted to verify the identified miRNA signatures but also to investigate other clinical relevant allergens to elucidate potential allergen-specific miRNA changes that could increase our understanding of the regulatory mechanisms in ACD.

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