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The proteomic skin profile of moderate-to-severe atopic dermatitis patients shows an inflammatory signature

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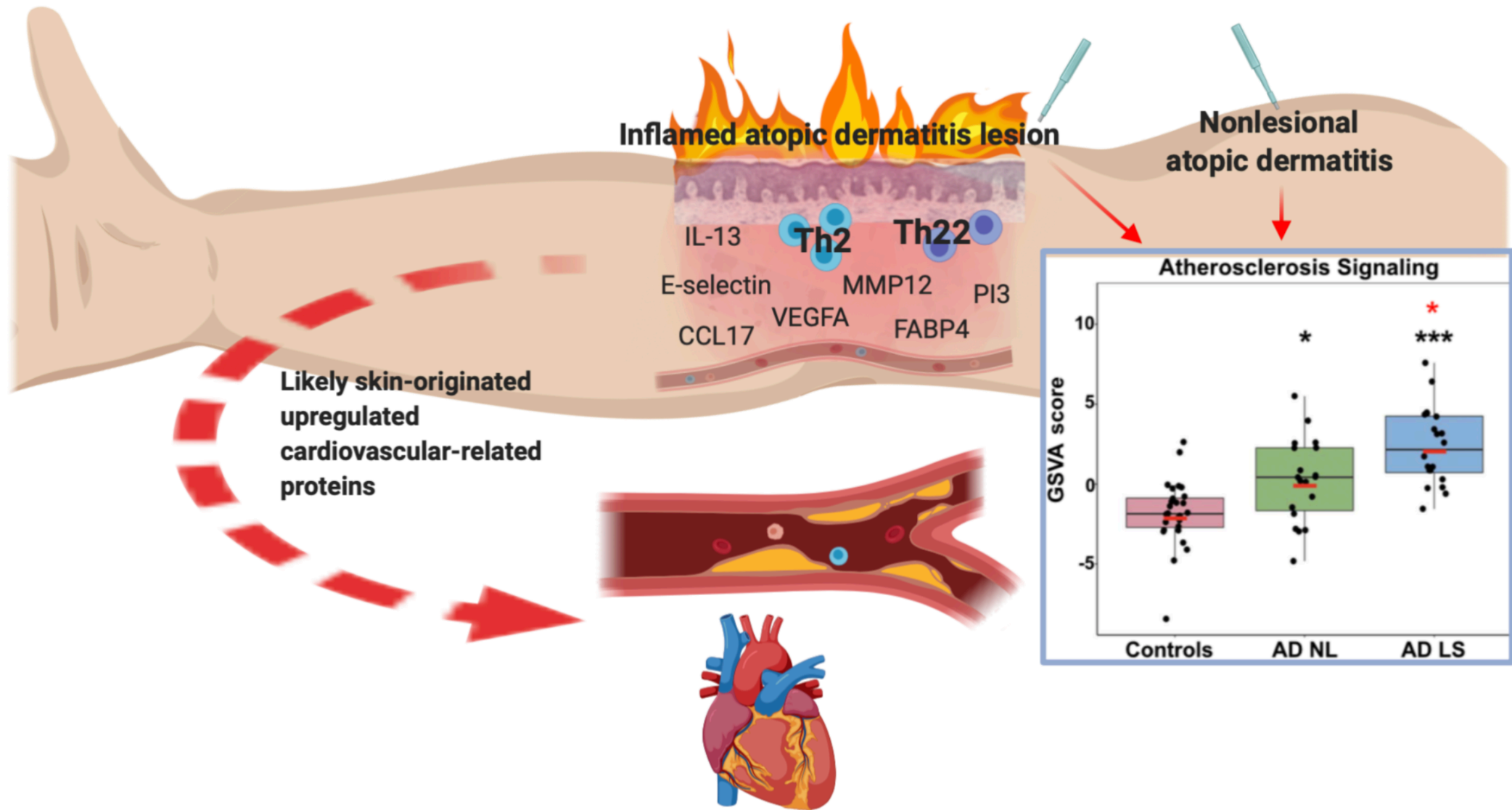
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Title: The proteomic skin profile of moderate-to-severe atopic dermatitis patients shows an inflammatory signature

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Abbreviations

AD: Atopic dermatitis

CVD: Cardiovascular disease

DEP: Differentially expressed protein

EASI: Eczema Area and Severity Index

FABP4: Fatty acid binding protein 4

FCH: Fold change

FDR: False discovery rate

GSVA: gene set variation analysis

HMOX1: heme oxygenase-1

IL: Interleukin

IL-1RL1: IL-1 receptor-like 1/IL-33R

LOX-1: Lectin-type oxidized LDL receptor 1

LTBR: Lymphotoxin-beta receptor

MCP-1: Monocyte chemoattract protein-1

MPO: Myeloperoxidase

OSM: Oncostatin M

PEA: Proximity extension assay

PGF: Platelet growth factor

82 RETN: Resistin

84 SELE: E-selectin

86 SCORAD: SCORing Atopic Dermatitis

87 TNFSF10/TRAIL: TNF-related apoptosis inducing ligand

89 VEGFA: Vascular endothelial growth factor A

93 CAPSULE SUMMARY

- 94 • Our proteomic data extend the “inflammation map” of atopic dermatitis, which
96 was created largely through gene expression profiling. It also suggests that risk
97 proteins found in blood are primarily derived from skin.
- 99 • Early treatment of skin inflammation may lower systemic immune or
100 cardiovascular-risk mediators in blood, potentially modifying disease co-
101 morbidities.

ABSTRACT

Background: Moderate-to-severe atopic dermatitis/AD is increasingly recognized as a systemic disease, largely due to proteomic blood studies. There are growing efforts to develop AD biomarkers utilizing minimal tissues.

Objective: To characterize the AD skin proteomic signature and its relationship with the blood proteome, and genomic skin profile in the same individuals.

Methods: We evaluated lesional and non-lesional biopsies and blood from moderate-to-severe AD (n=20) and healthy (n=28) individuals using OLINK proteomics (utilizing 10µg/10µL for skin and blood) and RNAseq (skin).

Results: The AD skin proteome demonstrated significant upregulation in lesional and even in non-lesional skin compared to controls in inflammatory markers (MMP12; Th2/IL1RL1/IL-33R, IL-13, CCL17; Th1/ CXCL10; Th17/Th22/PI3, CCL20, S100A12), and in cardiovascular-associated proteins (SELE, MMPs, PGF, MPO, FABP4, VEGFA; FDR<0.05). Skin proteins demonstrated much higher and significant upregulations (vs. controls) compared to blood, suggesting a skin source for the inflammatory/cardiovascular profile. Gene and protein expressions were correlated ($r=0.410$, $P<0.001$), with commonly upregulated inflammatory and cardiovascular-risk products, suggesting protein translation in skin.

Limitations: Our analysis was limited to 354 proteins.

Conclusions: The AD skin proteome shows an inflammatory and cardiovascular signature even in non-lesional skin, emphasizing the need for proactive treatment. Skin proteomics presents a sensitive option for biomarker monitoring.

INTRODUCTION

Atopic dermatitis (AD) is increasingly recognized as associated with higher risk for cardiovascular comorbidities,¹⁻⁵ likely due to persistent systemic inflammation.⁶⁻⁹

Current efforts to develop minimally invasive AD biomarkers are ongoing.¹⁰⁻¹⁵ Proteomic studies in blood using the OLINK Multiplex assay (requiring only 10µL serum) identified biomarkers reflecting AD severity and functional barrier measures,^{10, 11,12} highlighting systemic immune activation in adult¹¹ and even early-onset pediatric AD.¹⁰

Nevertheless, the molecular understanding of AD pathomechanisms is primarily based on skin studies. A comprehensive proteomic study in skin, with appropriate correlations with blood, is lacking. Only two cutaneous proteomic studies in AD have been performed, using tape-strips to evaluate a limited panel of inflammatory mediators in the stratum corneum in AD children.^{13, 14} Furthermore, some hallmark AD biomarkers (i.e IL-4, IL-13), typically highly elevated in whole-skin AD genomic signatures, were either not detected or showed down-regulation in these tape-strip studies.¹⁴ Thus, a comprehensive proteomic profile of whole-skin biopsies in AD compared to controls is lacking.

This study is the first to characterize the proteomic profile of lesional and non-lesional skin of moderate-to-severe adult AD patients, using a large panel of 354 markers measured with the high-throughput OLINK platform.

METHODS

Patients

We enrolled twenty moderate-to-severe AD adults (9 females, 11 males; mean age 40.6yrs; mean SCORAD 61.8, range 40.9-78; mean EASI 27.4, range 8.7-42.4), and twenty-eight healthy controls (13 females, 15 males; mean age 37yrs) (**Table I**).

Patients did not use topical treatments (corticosteroids, calcineurin antagonists or crisaborole) for ≥ 2 weeks, and phototherapy or systemic treatment such as dupilumab or other investigational drugs for ≥ 4 weeks prior to enrollment. There were no significant differences in demographics between patients and controls. Patients and controls did not report cardiovascular comorbidities; healthy controls had no atopic-related conditions. Patients had chronic AD since childhood. Severity scores included SCORing of Atopic Dermatitis/SCORAD and Eczema Area and Severity Index/EASI.

Biopsy collection

Lesional, non-lesional AD, and healthy skin punch biopsies were obtained under IRB-approved protocols. Non-lesional biopsies were obtained from vicinity of lesions, but ≥ 10 cm away from active lesions. Biopsied sites showed no evidence of infections. Most biopsies in both patients and controls were taken from the extremities (as AD most commonly affects the folds) and only if not feasible, from the trunk.

Skin and blood protein quantification

Skin biopsies were embedded in Tissue-Tek® Optimal Cutting Temperature (OCT) compound, grinded and centrifuged. 10 μ g protein was used for OLINK Proseek® multiplex ultrasensitive platform, using 4 panels: inflammation, cardiovascular/CVD II, CVD III, and neuro-inflammation (354 established and exploratory markers), as reported.^{10, 11, 16-19}

Blood was collected from the same study participants; 10 μ L serum was analyzed using the same OLINK panels, as described.^{10, 11, 17-19}

Gene expression analysis using RNA sequencing

RNA was extracted from the same biopsies and RNA-Seq was performed using Illumina HiSeq4000, as described.²⁰⁻²⁴

Statistical analyses

Analyses were performed using R-language (R-project.org) and Bioconductor Project packages (www.bioconductor.org), as described.^{10, 11, 18, 24} Protein and gene expression profiles were modeled by linear models using R's *limma* framework.²⁵ P-values from moderated (paired) t-tests were adjusted for multiple hypotheses using the Benjamini–Hochberg procedure to produce false discovery rates (FDRs). Proteins with fold changes (FCHs) > 2.0 and FDR < 0.05 were considered differentially expressed. A 21 protein subset linked with atherosclerosis-signaling,^{10, 11} was quantified using a gene-set variation analysis (GSVA).²⁶ Correlations between mRNA, protein, and severity scores in skin and blood were evaluated by Spearman correlations.

RESULTS

The proteomic AD skin profile shows increases in inflammatory and pro-atherogenic proteins

Twenty moderate-to-severe AD adults and twenty-eight healthy controls were included (**Table I**). The OLINK high-throughput proteomic multiplex platform evaluated 354 proteins from the inflammation, cardiovascular/CVD II, CVD III, and neuro-immunology panels,^{10, 11, 18, 27} in lesional and non-lesional AD and control skin. 161 of the 354 proteins were differentially expressed (FCH > 2 and FDR < 0.05) in lesional and 69 in non-lesional AD, compared to control skin (**Supplementary Table I**). The top 50

of these 161 differentially expressed proteins (DEPs) in AD skin are presented in a heat-map (**Fig 1**).

We observed elevations in protein markers of inflammatory cells, including dendritic cells (TNFSF10/TRAIL) and T-cell/T-cell activation (IL-2RA, CD40) in both lesional and non-lesional AD (FDR<0.05). We also observed significant upregulation of proteins associated with general inflammation (MMP12) and multiple immune axes, including Th2 (IL-13, IL1RL1/IL-33R, CCL13/CCL17), Th1 (CXCL9/CXCL10), and Th17/Th22 (PI3, CCL20, S100A12) in non-lesional and/or lesional AD (FDR<0.05) compared to controls.

The top significantly upregulated proteins in lesional and/or non-lesional AD skin compared to controls included multiple prognostic and/or therapeutic protein targets of atherosclerosis/cardiovascular risk (**Fig 1, Supplementary Table I**). These included potential biomarkers or therapeutic targets of atherosclerosis, such as E-selectin/SELE, matrix metalloproteinases/MMPs (MMP1/MMP3/MMP9), CCL19, CCL2, resistin/RETN, platelet growth factor/PGF, lectin-type oxidized LDL receptor 1/LOX-1 (or OLR1), myeloperoxidase/MPO, and fatty acid binding protein 4/FABP4 (FDR<0.05). We also found significant increases in innate cytokines/receptors (IL-6R, IL-8; FDR<0.05), which promote atherosclerosis.²⁸⁻³⁰ Transforming growth factor/TGF- β 1, involved in cardiac hypertrophy, vascular remodeling, and renin-angiotensin regulation,³¹ the vascular endothelial growth factor A/VEGFA, which mediates angiogenesis, and heme oxygenase-1/HMOX1, which protects against atherosclerosis,³² and the pro-apoptotic and potential heart failure target, caspase-3/CASP3, were upregulated in non-lesional and/or lesional skin (FDR<0.05; **Fig 1, Supplementary Table I**).

Remarkably, the non-lesional skin of AD patients demonstrated significant upregulation of inflammatory and atherosclerosis/cardiovascular risk proteins compared

to healthy skin (albeit smaller than in lesional skin), emphasizing the systemic nature of AD. This is emphasized by the gene-set-variation-analysis (GSVA) of 21 atherosclerosis signaling-specific proteins, showing significant upregulation of this subset^{10, 11} in both lesional and non-lesional AD versus control skin ($P < 0.05$; **Fig 2**).

In order to ascertain whether patients with AD and other atopic conditions have a different, and perhaps more inflammatory signature than patients with AD alone we also performed a sensitivity analysis comparing the two groups. This sensitivity analysis did not show significant differences between the two groups (**Supplementary Table II**).

AD skin demonstrates much higher expressions than blood

We next investigated whether the skin or blood compartments (via blood flow to skin) are the source of the upregulated inflammatory and atherosclerosis/cardiovascular-related proteins in AD skin, evaluating the relationship between skin and blood proteomics.

Overall, the differences between lesional AD and healthy skin were much larger than those between AD and control blood, as visualized by the marked predominance of markers on the right side of the scatterplot (**Fig 3**). The FCHs in lesional skin were not only larger, but also more significant than in blood. While 161 DEPs were found in lesional skin, only 1 DEP in blood fulfilled the $FCH > 2$ and $FDR < 0.05$ criteria, similar to prior reports.^{10, 11, 12} With a looser criteria ($FCH > 1.3$ and $P < 0.05$), not accounting for multiple hypotheses, 220 DEPs were detected in lesional skin and 20 DEPs in blood of AD versus controls (**Supplementary Table I**). 17 of the 20 blood DEPs overlapped with skin DEPs, suggesting that while skin proteomics captures the majority of the blood signature; this does not hold in the opposite direction. Among the 17 overlapping DEPs were proteins associated with Th2 (CCL13/CCL17), Th1 (CXCL9/CXCL10), and Th17

(PI3, CCL20) immune pathways ($P < 0.05$). MMP12 and IL-1RN, which binds IL-1R and inhibits IL-1 α/β signaling (which has been associated with cardiac disease and is being targeted in clinical trials)³³ were also differentially upregulated in both skin and blood ($P < 0.05$).

To understand how protein expression in skin and blood correlate, we conducted Spearman correlation analyses (**Supplementary Table III**). Proteins with significant skin-blood correlations were primarily those linked with cardiovascular risk. Markers of tissue remodeling (MMP3; $r = 0.544$), Th1 (CXCL11; $r = 0.469$), Th2 (CCL13; $r = 0.472$), and lymphoid chemoattraction (CCL19; $r = 0.469$) demonstrated significant correlations between blood and lesional expressions; endothelial cell adhesion (SELE; $r = 0.618$), T-cell activation (CD6, TREML2; $r = 0.514$, $r = 0.547$), and Th17-related (CCL20; $r = 0.644$) products were significantly correlated between non-lesional skin and blood ($P < 0.05$).

We also correlated protein expressions in skin with clinical severity (EASI/SCORAD) (**Supplementary Table IV**). In lesional, and particularly in non-lesional skin, we found significant correlations between expressions of cardiovascular/atherosclerosis-related markers and disease severity, including IL-18²⁸,²⁹ ($r = 0.448$, $p < 0.05$), angiotensin I converting enzyme 2/ACE2, which catalyzes cleavage of angiotensin and plays a role in regulation of cardiovascular and renal function ($r = 0.537$, $P < 0.05$) in lesional skin, and VEGFA ($r = 0.519$, $P < 0.05$) in non-lesional skin. In blood, FABP4 ($r = 0.475$), sortilin/SORT1 ($r = 0.552$), and HMOX1 ($r = 0.602$), which mediate lipid metabolism and are associated with atherosclerosis,³⁴⁻³⁶ significantly correlated with EASI ($P < 0.05$).

Integrating protein and mRNA expression measures in AD skin

Given that AD pathomechanisms were largely studied using transcriptomics,^{6, 16, 20, 24, 37, 38} we assessed the relationship between the AD skin proteome and transcriptome gene signature using RNAseq on the same biopsies. Since RNAseq covers many more genes, we limited our analysis to 339 markers, overlapping with OLINK measures.

Overall, protein and mRNA differences between AD vs. healthy skin significantly correlated in lesional ($r=0.410$, $P<0.001$, **Fig 4**) and non-lesional skin (data not shown). Genes with increased mRNA expressions frequently demonstrated concordant elevated protein levels, indicating local translation into protein. In lesional skin compared to controls, 83 of the 339 genes were differentially upregulated in RNAseq, whereas 160 of the 339 proteins were upregulated in OLINK. 59 gene products were commonly upregulated (**Supplementary Table I**). The markers with parallel protein and mRNA increases in lesional and/or non-lesional skin included inflammatory (IL-13, oncostatin-M/OSM) and cardiovascular risk/atherosclerosis measures such as IL-6, and MMPs, which also demonstrated significant protein and mRNA correlations (**Supplementary Table V**).

Several atherosclerosis/cardiovascular-related markers showed much higher protein than mRNA expressions in lesional versus control skin (**Fig 4**). These include SOD2, SELE, MPO, FABP4, CCL2, HMOX1, the serine protease PRSS27, and proteinase 3/PRNT3, which has pro-apoptotic and proinflammatory activity and is associated with heart failure post-myocardial infarction.³⁹ Some innate (IL-8), Th1- (CXCL9/CXCL10) and Th2- (CCL13) related markers also demonstrated greater protein expressions. Conversely, higher mRNAs compared to protein expressions were seen in

some products (FLT3LG, which regulates dendritic cells,⁴⁰ IL-6, IL-10, IL-20, IL-12/23p40, S100A12, CCL3).

DISCUSSION

This is the first evaluation of the proteomic signature of lesional and non-lesional skin in moderate-to-severe AD compared to healthy individuals. Two prior proteomic studies in tape-stripped skin from AD infants and children evaluated limited panels of 27 and 28 inflammatory mediators, with detection rates of 19/27, and 13/28, respectively.¹³ Furthermore, tape-stripping is limited to detection of biomarkers present in the outermost epidermis. In fact, key AD biomarkers (IL-4, IL-13), which are highly upregulated in transcriptomic analyses of AD whole-skin biopsies,^{6, 16, 20, 24, 37, 38} were either not detected or showed lower protein expression in AD compared to control tape-strips.^{13, 14}

Congruent with gene expression (or transcriptome) skin studies, that established AD pathomechanisms,^{6, 16, 20, 37, 38} our proteomic AD skin profile captures the inflammatory milieu in AD skin, including significant elevations in markers related to Th2 (IL-13, CCL17), Th22 (S100A12, Th1 (CXCL10) and Th17 (CCL20) pathways.

Among the top upregulated proteins in both lesional and non-lesional AD, we found increases in multiple atherosclerosis-associated proteins,^{10, 11} including CCL2, CCL19, SELE, PGF, LOX-1/OLR1, FABP4, MPO, MMPs, RETN, CASP3, TGF- β 1, and VEGFA. CCL2 or monocyte chemoattract protein-1 (MCP-1), is released from macrophages and endothelial cells, and overexpressed in atherosclerotic plaques.^{41, 42} The lymphoid-organizing chemokine, CCL19, has been shown to be upregulated in atherosclerotic plaques.^{43, 44} Levels of endothelial cell adhesion molecule, SELE, were associated with coronary artery disease (CAD),⁴⁵ PGF, a homologue of VEGF, has been linked to CAD

prognosis,³⁰ and anti-PGF antibodies inhibited atherosclerotic plaques in mice.⁴⁶ LOX-1/ORL1, is involved in critical steps of atherosclerosis.^{47, 48} Several anti-atherosclerotic drugs (statins, metformin, calcium channel blockers) inhibit LOX-1 signaling.^{47, 48} FABP4, a lipid metabolism mediator, is targeted in atherosclerosis and diabetes.^{48, 49} MPO is produced by neutrophils, monocytes, and macrophages, and catalyzes LDL modification. Elevated MPO levels are associated with CAD,⁵⁰ and plasma MPO is an early risk predictor of myocardial infarction.⁵¹ MMPs are implicated in vascular tissue remodeling,⁵² and atherosclerosis. RETN, is associated with obesity, type 2 diabetes and cardiovascular disease.⁵³ Caspase-3 inhibition is investigated for treatment/prevention of heart failure.⁵⁴ TGF- β 1 is involved in cardiac hypertrophy, and renin-angiotensin regulation.³¹ TGF- β 1 polymorphisms are correlated with hypertension,⁵⁵ and hypertensive patients have higher TGF- β 1.⁵⁶ VEGFA, a mediator of angiogenesis, was also increased in AD.⁵⁷

Several key atherosclerosis/cardiovascular risk-associated proteins in lesional and/or non-lesional skin were also significantly correlated with disease severity, including IL-18, VEGFA, and ACE2, which regulates cardiovascular and renal function.⁵⁸ The significant upregulations in inflammatory and atherosclerosis/cardiovascular-associated proteins in non-lesional AD skin, together with the more significant correlations between severity and non-lesional compared with lesional protein expressions, emphasize the systemic nature of AD.

To investigate the primary origin of these inflammatory, and atherosclerosis/cardiovascular risk proteins (whether they originate from the skin and then leak to blood, or initiate in blood and are distributed to skin through the blood supply), we evaluated the relationship between lesional skin and blood proteomics. Our findings suggest that the skin is likely the source of these upregulated proteins, as their protein expressions in

AD lesions were significantly larger compared to blood levels. Further, the skin proteomic signature captured many more markers than the blood profile, consistent with prior serum reports.^{21,22} The limited number of correlations between blood and skin proteomics also implies that the elevated skin proteins are not simply deposited by the blood supply. Instead, it is more likely that the protein is leaking from skin into blood.

We also evaluated the differences between mRNA and protein expressions in lesional AD. Although the transcriptomic AD profile was extensively studied,^{6, 16, 20, 21, 37, 38, 59, 60} there has been no investigation into whether the mRNA is ultimately translated into protein. Overall, mRNA and protein expressions were significantly correlated, indicating local translation of protein in the skin. This again suggests skin as the primary source for the upregulated proteins. Many protein and gene products were differentially upregulated in lesional skin in both OLINK and RNAseq platforms. These included atherosclerosis-related proteins such as IL-6, MMPs, SELE, Oncostatin-M/OSM, and the IL-33 receptor, ST2/IL1RL1. OSM was suggested as a biomarker of atherosclerosis, with elevated OSM serum levels significantly correlated with coronary stenosis.^{61, 62} The IL-33/ST2 pathway plays a dual role in Type 2 inflammation and in cardiovascular disease.⁶³ Clinical trials for IL-33 (NCT03533751) and OSMR (NCT03754309) showed preliminary efficacy in moderate-to-severe AD adults,^{64, 65} and may also benefit patients at risk for cardiovascular comorbidities.

Several atherosclerosis/cardiovascular markers showed much higher protein rather than mRNA expression, including SELE, MPO, FABP4, HMOX1, and PRNT3, which is associated with heart failure.³⁹ This could be attributed to accumulation of protein due to a longer half-life or an amplifying effect leading to increased translation. There were also some gene products that showed higher mRNA rather than protein expression, including FLT3LG, IL-6, IL-10, IL-20, IL-12/23p40, S100A12, and CCL3.

These proteins may be either less stable than the mRNAs and thus degrade quickly, or are being consumed through binding and uptake by receptors. In this case, a lack of protein would not necessarily imply lack of function; they could be mediating strong signaling through receptor binding, which subsequently results in decreased levels.

One limitation of our study is the fact that our proteomic analysis was limited to 354 markers. Nevertheless, this is the first proteomic study in biopsies, and the largest in skin. Another limitation is that blood mRNA is not available; however, the proteomic studies in blood support the skin as the primary source of inflammatory proteins.

Overall, this study identified the adult AD proteomic signature in skin biopsies.¹⁴ Future studies should attempt to also validate this method in children and in longitudinal studies. The increased atherosclerosis/cardiovascular risk-associated proteins in AD lesional and even in the “visibly normal-appearing” (non-lesional) skin emphasize the importance of proactive treatment. Our data suggest that the skin rather than blood is the primary source for the inflammatory and atherosclerosis/cardiovascular signature. The proteomic skin profile can be valuable for future studies requiring close biomarker monitoring. This is particularly important considering that OLINK platform requires as little as 10µg per tissue, which can be easily acquired through as little as a 1mm punch biopsy (or 10µL serum).

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Table I. Baseline patient demographics.

Characteristics	Atopic dermatitis	Controls	P-value
No. of patients	20	28	—
Age (years)			
Mean ($\pm$ SD)	40.6 ($\pm$ 15.5)	37 ($\pm$ 11.1)	0.39
Median, (Range)	37 (23-66)	38.5 (18-57)	
Sex, no.			
Female	9	13	0.1
Male	11	15	
Clinical Severity Scores			
SCORAD			
Mean ($\pm$ SD)	61.8 ($\pm$ 12.3)	—	—
Median, (Range)	62 (40.9-78)	—	—
EASI			
Mean ($\pm$ SD)	27.4 ($\pm$ 9.9)	—	—
Median, (Range)	27.4 (8.7-42.4)	—	—
IgE			
Mean ($\pm$ SD)	3572 ($\pm$ 10682)	—	—
Median, (Range)	355 (12-48390)	—	—
No. of patients with other atopic conditions	8	—	—

AD, atopic dermatitis; *SCORAD*, SCORing of atopic dermatitis; *EASI*, Eczema Area and Severity Index; *SD*, standard deviation.

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Figure Legends

Figure 1. Heatmap representing the top 50 of 161 differentially expressed proteins (DEPs) in atopic dermatitis (AD) lesional skin compared to healthy skin, using criteria of $FCH > 2$ and $FDR < 0.05$. Table shows up-regulated markers and respective fold changes in non-lesional (NL) AD and lesional (LS) AD versus normal skin, and in LS AD versus NL AD skin. * $FDR < 0.05$; ** $FDR < 0.01$.

Figure 2. Atherosclerosis signaling pathway. A gene-set-variation-analysis (GSVA) of 21 atherosclerosis signaling-specific proteins, showing significant increases in z-scores of atherosclerosis proteins in non-lesional and lesional AD compared to normal skin. * $P < 0.05$; *** $P < 0.001$. *Black stars*: significance of comparison between AD skin and normal skin; *red star*: significance of comparison between AD lesional skin versus non-lesional skin.

Figure 3. OLINK proteomics in blood compared to skin from moderate-to-severe AD patients. Scatter plots depicting $\log_2$ fold-change proteomic differences in blood (y-axis) and lesional skin (x-axis) from AD patients compared to healthy controls; the size of the circles represents the absolute difference (in $\log_2$ fold-changes) between protein expressions of AD vs control subjects in skin and blood.

Figure 4. OLINK proteomics versus gene expression analysis using RNA-sequencing in lesional atopic dermatitis (AD) vs. control skin. Scatter plots depicting $\log_2$ fold-changes in the same AD patients compared to their respective controls using OLINK proteomics and RNAseq gene expression profiling; the size of the

636 circle represents the absolute difference (in $\log_2$ fold-changes) between AD and control
637 subjects in OLINK and RNA-sequencing.

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Figure 1

Top 50 differentially expressed proteins in AD skin

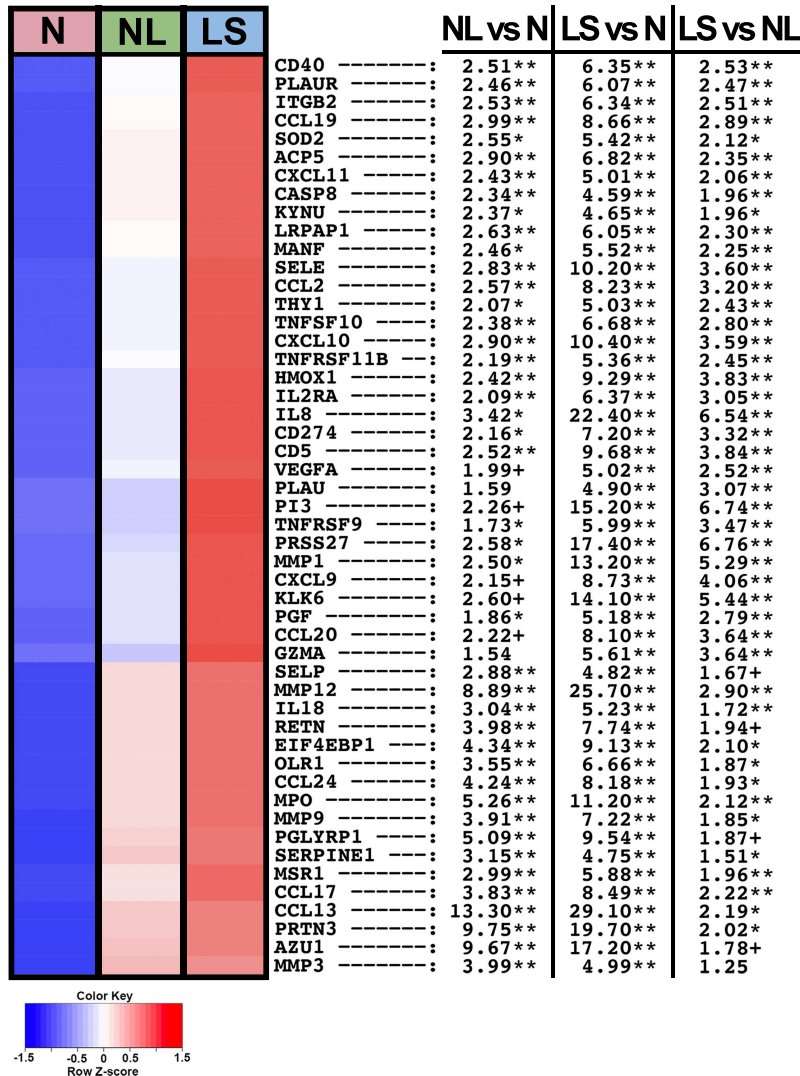


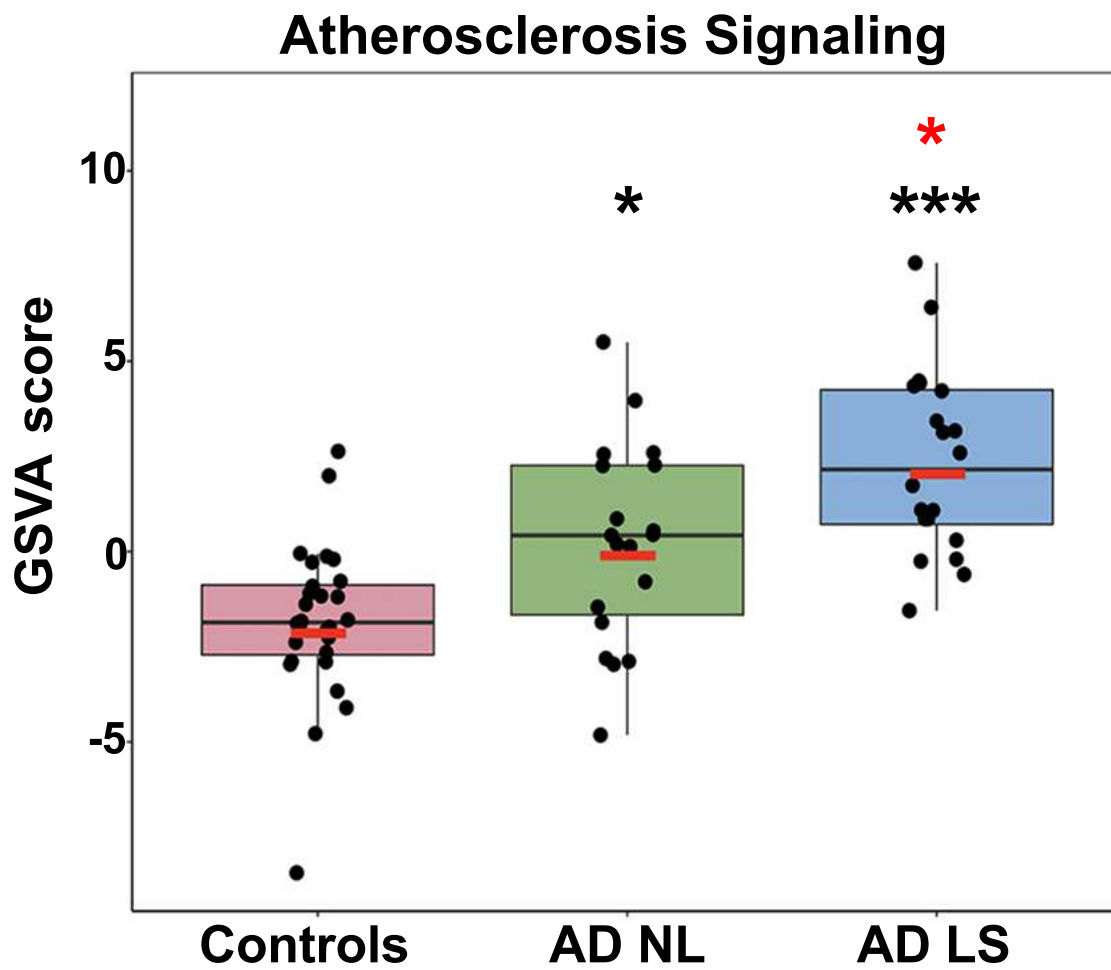
Figure 2

Figure 3

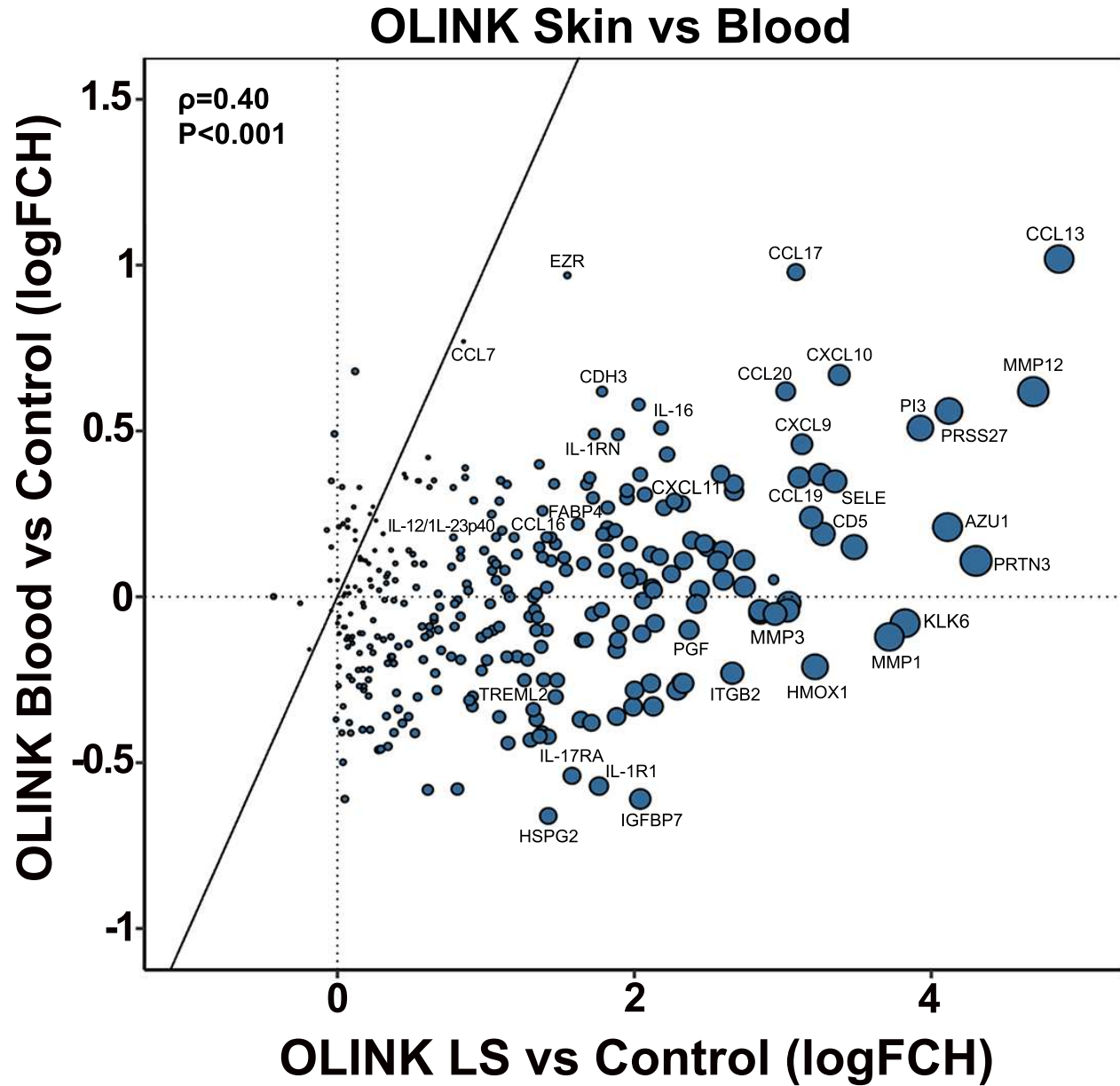
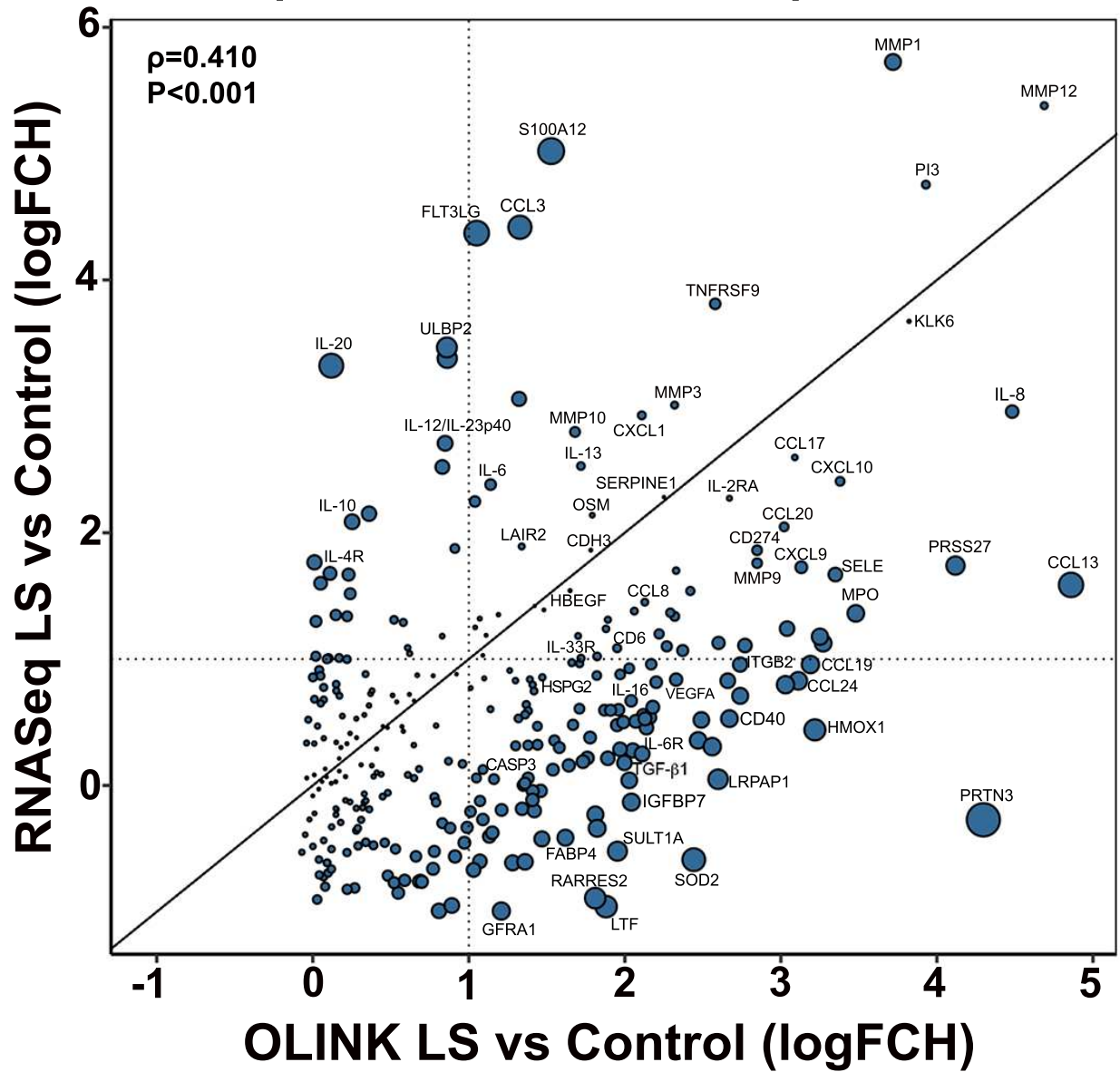


Figure 4

RNASeq mRNA levels vs OLINK proteins in skin



CAPSULE SUMMARY

- Our proteomic data extend the “inflammation map” of atopic dermatitis, which was created largely through gene expression profiling. It also suggests that risk proteins found in blood are primarily derived from skin.
- Early treatment of skin inflammation may lower systemic immune or cardiovascular-risk mediators in blood, potentially modifying disease co-morbidities.