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Proteomic analysis of cardiovascular disease-associated proteins in Korean patients with moderate-to-severe atopic dermatitis

Seon-Pil Jin, MD, PhD[a,b,c,1], Hosu Kim, MD[d,1], Ji Hwan Moon, PhD[e,1], Seunghee Kim-Schulze, PhD[f], Yookyung Sophie Chun, BS[g], Hyo Jeong Nam, BS[g], Yoon Ji Bang, BS[g], Ji Su Lee, MD, PhD[a,b,c], Jung Eun Kim, MD, PhD[h], Chung-Gyu Park, MD, PhD[d,g,i,j], Hyun Je Kim, MD, PhD[d,g,i,j]** and Dong Hun Lee, MD, PhD[a,b,c]*

ABSTRACT

Background: Cardiovascular diseases (CVDs) have been associated with atopic dermatitis (AD), including in Korean patients. Previous studies on AD have primarily focused on patients of European ancestry, while the Asian endotype exhibits distinct characteristics. This study aimed to characterize the blood proteomic signature of Korean patients with moderate-to-severe AD, with an emphasis on proteins related to CVDs.

Methods: A total of 78 participants, including 39 patients with moderate-to-severe AD and 39 age- and sex-matched healthy controls, were enrolled. Blood proteomics analysis was performed using the Olink CVD II panel, which measures the expression levels of 92 proteins associated with CVDs.

Results: Unsupervised hierarchical clustering revealed 44 upregulated and 5 downregulated proteins in AD patients compared to healthy controls. Principal component analysis (PCA) effectively distinguished AD patients from healthy subjects based on the complete set of proteins or the subset of upregulated proteins. A multiple linear regression model comprising CCL17 and FGF21 showed a strong correlation with disease severity ($R = 0.619$). Correlation analysis identified 25 highly correlated proteins, including STK4, ITGB1BP2, and DECR1, which were newly found to be upregulated in Korean AD patients. Pathway analysis highlighted the involvement of these proteins in vascular system, inflammation, and lipid metabolism pathways.

Conclusion: The blood proteomic profile of moderate-to-severe AD patients in Korea differed from healthy controls using the CVD II panel. This study provides potential biomarkers for the AD-CVD association and insights into the pathways contributing to this relationship in the Korean population.

Keywords: Atopic dermatitis, Proteomics, Korean patients, Cardiovascular diseases

[a]Department of Dermatology, Seoul National University Hospital, Republic of Korea
*Corresponding author. Department of Dermatology, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea. E-mail: ivymed27@snu.ac.kr
**Corresponding author. Department of Microbiology and Immunology, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea. Email: hjkim0518@gmail.com
[1] Equally contributed.
Full list of author information is available at the end of the article

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BACKGROUND

Atopic dermatitis (AD) is a common inflammatory skin disorder found in up to 5% of adults and 20% of pediatric populations worldwide.[1–3] AD can negatively affect patients' quality of life and is associated with comorbidities such as asthma, food allergies, depression, and anxiety.[4–6] The disease severity varies from individual to individual, and severe AD patients have been reported to have a higher risk of developing cardiovascular diseases (CVDs).[7–9] While AD-associated cardiovascular risk factors such as obesity and sleep disturbance could indirectly contribute to CVD pathogenesis in AD patients, specific biomarkers indicative of CVD development in severe AD patients remain elusive.[7] In addition, Asian AD endotype characteristics differ from those of other endotypes;[10–13] however, most studies have focused on patients of European ancestry. Therefore, we decided to investigate CVD-related protein markers of AD patients in Korea through a comparative analysis of AD patients and healthy individuals using the proteomic platform Olink multiplex assay.

To identify AD-specific CVD biomarkers, measuring the expression levels of proteins with known or potential association with CVD could yield a specific set of proteins upregulated in moderate-to-severe AD. [14–18] By utilizing the CVD II panel, studies have identified upregulated proteins such as CCL17, MMP12, IL16, FGF21, and LOX1 in AD patients.[14,17–20] In this study, we explored the novel proteomic signatures of AD patients in Korea, which have not been previously reported in studies involving other ethnic groups.

METHODS

Patient recruitment

Thirty-nine patients with moderate-to-severe AD and 39 age- and sex-matched healthy volunteers were recruited from 2 independent academic medical centers in South Korea. Subsequently, AD patients were clinically assessed for eczema area and severity index (EASI) scores. The study design received prior approval from the Institutional Review Boards (H-1908-031-1052 and PC22SISI0076) in accordance with the Declaration of Helsinki before the study's commencement. Following the approved study design, we collected informed consent from all study subjects. Blood samples were drawn from AD patients and healthy volunteers for blood proteome.[14]

Blood proteomic analysis

Blood proteomics data were generated using the Olink multiplex platform (Olink Bioscience, Uppsala, Sweden), which utilizes proximity extension assay (PEA) technology for high-throughput and sensitive biomarker detection. The CVD II panel was employed, consisting of 92 proteins with known or potential associations with human CVDs.[14,17,18,20,21] In the present study, we measured the expression levels of these 92 proteins in the blood plasma samples of 39 Korean patients with moderate-to-severe AD and 39 healthy volunteers using the Olink CVD II panel. The detected proteins were quantified and normalized to minimize technical variation. We analyzed the data as mentioned in the following section.

Data analyses

Statistical analyses were performed using Python version 3.10.5 (Python.org) and JASP version 0.16.3 (jasp-stats.org). Multiple linear regression analyses were performed using R version 4.2.3.[22] Multicollinearity diagnostics were computed with JASP. Principal component analysis (PCA) was performed using the *PCA* package in Python. *Seaborn* was used to draw a heatmap of protein expression levels, boxplots, and unsupervised hierarchical clustering, while *Numpy* was used to perform correlation analysis. The extraction of elevated or decreased proteins from AD patients was performed using a *t*-test, and multiple testing was corrected by the Benjamini-Hochberg adjustment method. Subsequently, the proteins with an adjusted *P* value of less than 0.05 were compiled in a list. The correlation analysis utilized the clustering technique and a correlation coefficient of 0.6 as the threshold. Gene ontology (GO) terms and pathway enrichment analyses were performed using DAVID from the Frederick National Laboratory[23] and Enrichr.[24]

RESULTS

The patient demographics and CVD II panel

The baseline characteristics of 39 patients with AD and 39 healthy volunteers are shown in Table 1. The ages of the subjects ranged from 19 to 60 for both groups. The male-to-female ratio was similar in both groups, with male dominance of 79.5% and 71.8% in AD and healthy volunteers, respectively. The mean EASI score was 24.8 ± 10.5. Blood samples from both AD patients and healthy volunteer groups were analyzed using the proteomics platform described in the Methods in order to identify potential biomarkers associated with the relationship between AD and CVD.

Protein expression levels proved sufficient for distinguishing AD patients from Healthy Control

Fig. 1A illustrates the visualization of the expression levels of CVD II proteins based on unbiased hierarchical clustering. Clustering revealed a separation between the AD and healthy control (HC) groups. Differentially expressed proteins were identified with an adjusted *P* value of less than 0.05. Forty-four proteins were upregulated in AD patients compared with HC, including 6 pro-inflammatory cytokines and chemokines: IL6, CCL17, IL16, CCL3, IL18, and IL17D. In contrast, 5 proteins, PRELP, ADAMTS13, RAGE, CTRC, and VEGFD, were downregulated in AD patients. The *P* values and log2 fold change values of the upregulated and downregulated proteins are shown in Fig. 1B. As demonstrated in Fig. 2, we performed PCA analyses to distinguish AD patients from healthy volunteers using proteomics data. Fig. 2A displays 2 distinct clusters consisting of AD patients and healthy volunteers. Moreover, we selected 44 upregulated and 5 downregulated proteins observed in Fig. 1B for additional PCA analyses. With 44 upregulated proteins, we could replicate the distinct clusters seen in Fig. 2A; however, with only 5 downregulated proteins, it was difficult to distinguish the patients from HC, as expected. The outcomes are depicted in Fig. 2B and C.

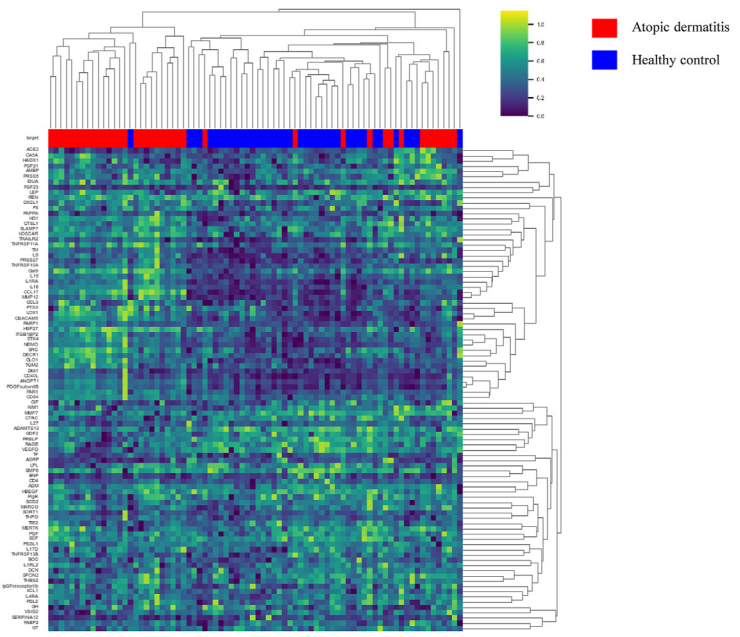
Proteins associated with CVD are highly correlated with AD disease severity

As disease severity could influence protein expression levels, we performed multiple linear regression analyses to detect proteins whose expression levels were correlated with disease severity.[25] We first performed multicollinearity diagnostics and removed 16 highly correlated proteins from the CVD II panel to resolve multicollinearity. ADAMTS13, HSP27, PDGF subunit B, IL16, PRELP, PRSS8, RAGE, SERPINA12, SORT1, TM, THPO, IL18, IL27, BNP, IL1RL2, and HAOX1 were excluded from the multiple linear regression analysis (condition index >20).[26] The

Patient Characteristics		n (%) or median [range]		
		AD patients $n = 39$	Healthy Controls $n = 39$	*P* value
Male (%)		31 (79.5%)	28 (71.8%)	0.435
Female (%)		8 (20.5%)	11 (28.2%)	
Age (years)		31 [19, 60]	31 [21, 56]	0.926
Medical data[a]	CsA	10 (25.6%)	–	–
	MTX	4 (10.3%)		
EASI score		24.8 ± 10.5	–	–
Disease Duration (years)		19 [1, 40]	–	–

Table 1. Patient baseline characteristics. [a]*Most patients were on medication of either topical steroid, calcineurin inhibitor and/or oral antihistamine. The proportion of patients taking systemic immunosuppressants (cyclosporine A or methotrexate) is indicated. AD, atopic dermatitis; CsA, cyclosporine A; EASI, eczema area and severity index; MTX, methotrexate.*

(A)



(B)

Protein Name	Log2 Fold Change	P value	Upregulated or downregulated	Protein Name	Log2 Fold Change	P value	Upregulated or downregulated
IL6	0.82079854	8.333E-09	Upregulated	THPO	0.15193725	2.029E-04	Upregulated
STK4	0.48173594	1.985E-03	Upregulated	GLO1	0.15159220	4.739E-08	Upregulated
CCL17	0.45040840	4.535E-22	Upregulated	PAR1	0.12755249	3.227E-09	Upregulated
CD40L	0.43186326	2.936E-04	Upregulated	IL17D	0.12666936	4.549E-02	Upregulated
IL16	0.40129264	6.233E-15	Upregulated	CD84	0.11910315	5.532E-04	Upregulated
CEACAM8	0.39083118	1.451E-08	Upregulated	Gal9	0.10173490	1.545E-10	Upregulated
CA5A	0.37921374	4.549E-02	Upregulated	HSP27	0.10074583	4.143E-04	Upregulated
IL1RA	0.36852507	4.233E-10	Upregulated	PRSS27	0.10035588	5.395E-04	Upregulated
MMP12	0.35869902	1.214E-12	Upregulated	TNFRSF11A	0.07540431	1.244E-04	Upregulated
TNFRSF10A	0.27198850	1.829E-08	Upregulated	HO1	0.07179341	1.641E-07	Upregulated
PARP1	0.26333587	1.297E-02	Upregulated	Dkk1	0.06707077	3.293E-03	Upregulated
SLAMF7	0.26094718	5.395E-04	Upregulated	TM	0.06195103	1.947E-06	Upregulated
PTX3	0.26052297	3.124E-03	Upregulated	REN	0.06124029	3.179E-02	Upregulated
IgG Fc receptor IIb	0.22459454	7.478E-03	Upregulated	TRAILR2	0.05876168	1.080E-03	Upregulated
LOX1	0.22408486	4.405E-05	Upregulated	PRSS8	0.05093904	2.255E-03	Upregulated
DECR1	0.22066337	6.970E-03	Upregulated	hOSCAR	0.04916736	9.834E-06	Upregulated
ANGPT1	0.21688160	1.535E-05	Upregulated	CTSL1	0.04173295	8.395E-03	Upregulated
NEMO	0.21446229	2.022E-05	Upregulated	MARCO	0.03887208	7.372E-04	Upregulated
PDGF subunit B	0.19467158	2.107E-04	Upregulated	AMBP	0.02648620	5.324E-03	Upregulated
CCL3	0.19213445	1.169E-03	Upregulated	PRELP	-0.02220019	6.800E-04	Downregulated
IL18	0.18083056	8.361E-09	Upregulated	ADAMTS13	-0.02509512	2.827E-03	Downregulated
TGM2	0.17462830	1.080E-03	Upregulated	RAGE	-0.03633028	3.757E-03	Downregulated
SRC	0.16696987	6.042E-03	Upregulated	CTRC	-0.05422965	8.621E-03	Downregulated
ITGB1BP2	0.16415222	6.970E-03	Upregulated	VEGFD	-0.06621488	1.099E-03	Downregulated
IL4RA	0.15425450	8.621E-03	Upregulated				

Fig. 1 Protein subsets with increased and decreased expression levels are identified in AD. (A) Heatmap of AD patients with healthy controls. AD patients and healthy controls are listed at the top according to the unsupervised hierarchical clustering and denoted according to the group: red, AD patients; blue, healthy controls. The unsupervised hierarchical clustering of the proteins is shown in the right corner. Expression levels were color-coded according to normalized expression values, as indicated in the vertical legend. Light green indicates higher expression levels and dark green indicates lower expression levels. (B) The upregulated and downregulated proteins with statistically significant (adjusted $P < 0.05$) are listed along with their P values in scientific notation (E = exponent) and log2 fold change values. P values were adjusted using the Benjamini-Hochberg multiple testing correction methods. AD, atopic dermatitis. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article)

multiple linear regression models computed after the exclusion are shown in Fig. 3A. The regression model consisting of CCL17 and FGF21 was considered the best (R = 0.619). The model with CCL17 alone was the second best, with R = 0.543. CCL17 and FGF21 had significant P values as coefficients ($P < 0.001$ and 0.029, respectively). A scatter plot depicting the linear relationship between CCL17 and EASI scores is shown in Fig. 3B.

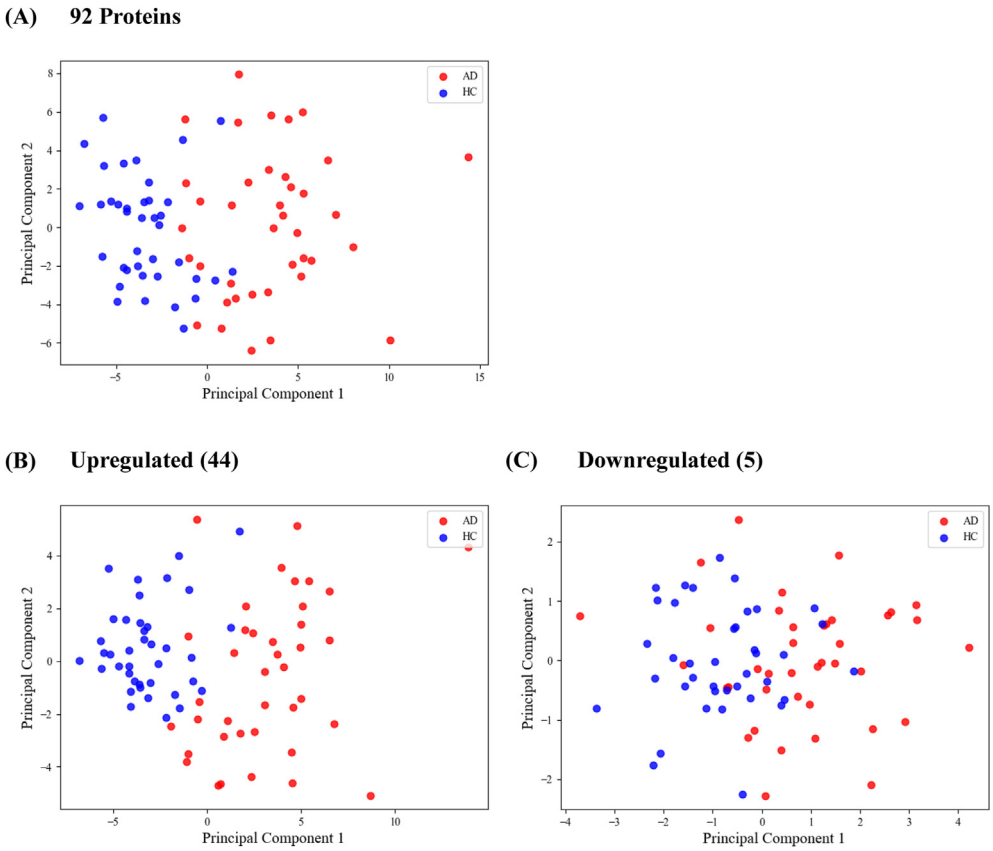


Fig. 2 The CVD II panel and its subsets of upregulated proteins effectively distinguish AD from healthy controls. Each red and blue dot represents a patient with AD or a healthy volunteer, respectively. (A) The PCA was drawn using 92 proteins. (B) Forty-four upregulated proteins were used to compute the PCA. (C) Five downregulated proteins were used for the PCA. AD, atopic dermatitis; CVD, cardiovascular disease; PCA, principal component analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article)

A distinct set of proteins, including STK4, DECR1, and ITGB1BP2, demonstrates a strong correlation with the other upregulated proteins of moderate-to-severe AD patients in Korea

We attempted to uncover a group of proteins that were highly correlated with each other in AD patients. To identify a specific pathway or cellular process pertinent to AD disease activity, a group of correlated proteins was examined using Pearson correlation analysis (Fig. 4A). Correlation analysis yielded 25 proteins with highly correlative expression levels: CD84, CD40L, ANGPT1, PDGF subunit B, PARP1, GLO1, DECR1, ITGB1BP2, SRC, STK4, NEMO, TNFRSF10A, PAR1, PRSS27, Gal9, IL18, CCL17, MMP12, IL1RA, IL16, PTX3, LOX1, CEACAM8, TGM2, and Dkk1. Correlation coefficients and hierarchical clustering were used to compute the results. Notably, all 25 proteins were upregulated in Fig. 1B.

Most of the 25 proteins that were highly correlated with each other have been mentioned in previous studies for their association with AD. Fig. 4B shows a list of proteins from the CVD II panel extensively studied in Olink studies.[14–20,27] However, the literature has scarcely mentioned STK4, DECR1, and ITGB1BP2. To further investigate, their expression levels were compared between AD patients and healthy volunteers by drawing box plots (Fig. 4C). The difference in expression levels between the AD and HC groups was statistically significant for each protein (STK4, $P < 0.001$; DECR1 and ITGB1BP2, $P < 0.01$).

Pathway analysis of 25 highly correlated proteins implies potential CVD pathogenesis associated with AD

Pathway enrichment analysis of the 25 proteins was conducted using Enrichr to examine the CVD-associated proteins further in AD patients. The significantly enriched pathways are illustrated in Fig. 5. Enrichment primarily indicated involvement in cell surface interaction at the vascular wall, hemostasis, and angiogenesis, suggesting an

(A) Multiple linear regression summary

Model Summary			
Model	R	R^2	RMSE
CCL17	0.543	0.294	8.961
CCL17, FGF21	0.619	0.383	8.497
Model Equation			
CCL17	Y = -27.798 + 0.048(CCL17)		
CCL17, FGF21	Y = -38.564 + 0.049(CCL17) + 0.017(FGF21)		

RMSE, root-mean-square-error; CCL17, C-C motif chemokine ligand 17; FGF21, fibroblast growth factor 21

(B)

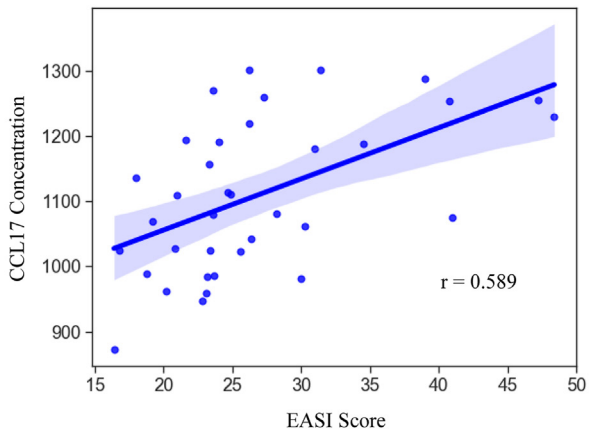


Fig. 3 Proteins associated with CVD in AD patients highly correlate with disease severity. (A) Multiple linear regression model displays the linear relationship between the proteins and the EASI score. Out of 92 proteins in the panel, those with multicollinearity (condition index >20) were excluded before conducting analysis. (B) The scatter plot displays the relationship between CCL17 expression levels and EASI scores. AD, atopic dermatitis; CCL17, CC chemokine ligand 17; CVD, cardiovascular disease; EASI, eczema area and severity index

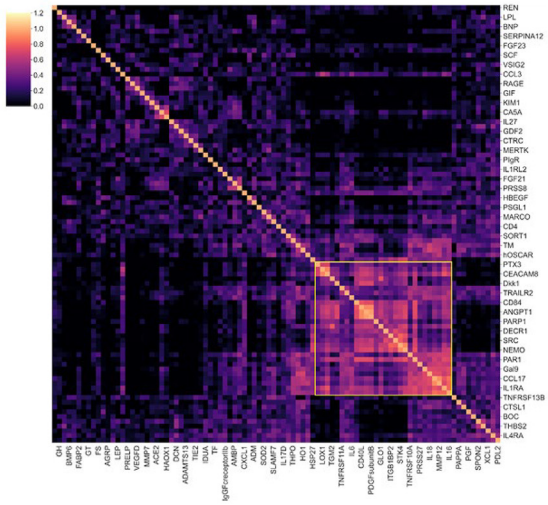
association with the vascular system. Inflammatory response, cytokine-cytokine receptor interactions, and positive regulation of interleukin-6 production were indicative of involvement in the inflammatory process. Additionally, "lipid and atherosclerosis" and "leptin signaling pathway" further emphasized their involvement in lipid metabolism. Overall, we identified the biological processes reflected in the 25 upregulated proteins from the CVD II panel, which exhibited high correlation among themselves, implying the pathomechanisms of CVD within AD patients.

DISCUSSION

The association between AD and CVD has been controversial; however, further supporting studies have indicated a strong association between AD and CVD.[7-9,28] Moreover, a recent epidemiological study utilizing Korean national health insurance data confirmed the association between AD and CVD in AD patients in Korea.[28] While the link between AD and CVD has been supported, the exact pathomechanisms that foster CVD development in AD patients remain poorly understood.

Previous epidemiological and cohort studies have provided limited insights regarding the exact CVD pathomechanisms in AD [7-9,28] On the other hand, AD proteomics data can help reveal additional insights concerning CVD pathogenesis in AD patients.[14,20] For instance, inflammatory markers such as MMP12 were revealed to be

(A)



(B)

Proteins previously reported in AD but not in Olink study	Proteins previously reported in the AD Olink proteomics studies	Newly identified proteins in the current study
Dkk1	MMP12	DECR1
ANGPT1	CCL17	STK4
GLO1	CD40L	ITGB1BP2
PAR1	IL16	
PTX3	LOX1	
TGM2	PRSS27	
SRC	IL18	
CD84	IL1RA	
	Gal9	
	PARP1	
	PDGF subunit B	
	TNFRSF10A	
	CEACAM8	
	NEMO	

(C)

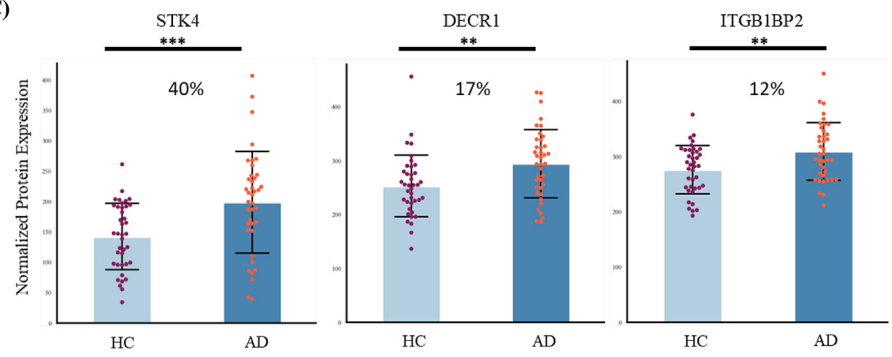


Fig. 4 The distinct protein set exhibits a strong correlation, with STK4, ITGB1BP2, and DECR1 showing significant upregulation in AD patients in Korea. (A) Heatmap for Pearson correlations between protein expression levels. The correlations were color-coded according to the vertical color map based on their computed correlation coefficient values. Orange indicates higher correlations, and violet indicates lower correlations. The yellow box includes a cluster of 25 proteins with high correlations. The proteins were first categorized using unsupervised hierarchical clustering and had to report a correlation coefficient greater than 0.6 with proteins other than themselves. The proteins were labeled alternatively on either the vertical or horizontal axis of the heatmap. (B) Correlating proteins previously mentioned in the non-Olink studies for AD are listed in the left column. The correlating proteins previously reported to be upregulated in the AD Olink studies are listed in the center column. The correlating proteins newly identified in this study are listed in the right column. (C) Box plots were drawn to compare the expression levels of the newly identified proteins, STK4, ITGB1BP2, and DECR1, in the AD patients and the healthy volunteers. An asterisk denotes statistical significance with $^{**}P < 0.01$, $^{***}P < 0.001$. AD, atopic dermatitis; CCL17, CC chemokine ligand 17; CVD, cardiovascular disease; EASI, eczema area and severity index; STK4, Serine Threonine Kinase 4; ITGB1BP2, integrin subunit beta 1 binding protein 2; DECR1, 2, 4 dienoyl-CoA reductase (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article)

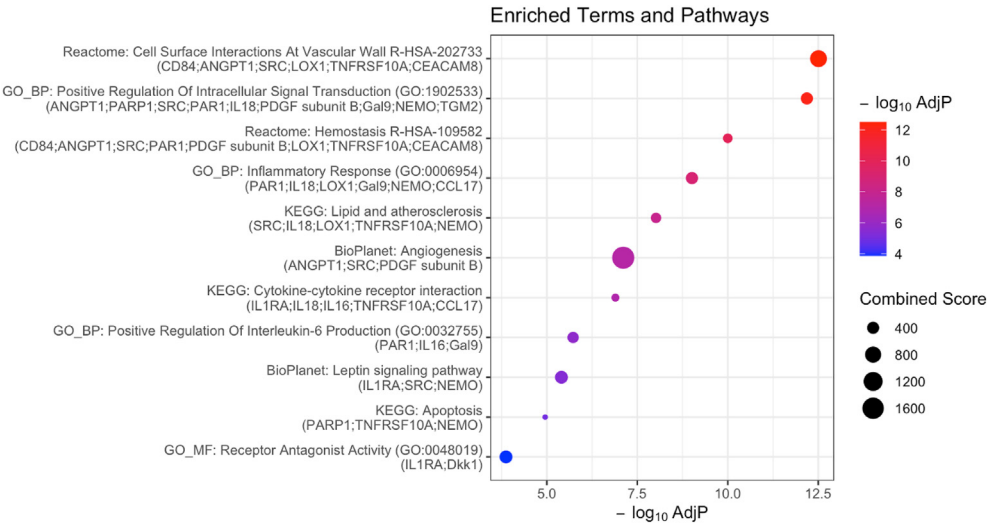


Fig. 5 Pathway and GO analyses identified pathways enriched in relation to CVD within AD patients. Bubble plot of GO and various pathway enrichment analyses (Reactome Pathway Database, GO terms including GO_MF, GO_BP, KEGG, BioPlanet) of the 25 proteins from the CVD II panel. The X-axis represents the -log adjusted *P* value (-log 10 AdjP). Color displays -log10 adjusted *P* value; closer to red indicates more significant enrichment. The bubble size represents the enrichment score. GO, gene ontology; GO_MF, GO molecular function; GO_BP, GO biological process; KEGG, Kyoto Encyclopedia of Genes and Genomes; CVD, cardiovascular disease; AD, atopic dermatitis. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article)

elevated in non-lesional and blood proteomics data, indicating that AD-associated inflammation and immune dysregulation are systemic in nature.[14] However, recent efforts have primarily focused on AD patients of European ancestry.[14–20] Including AD patients in Asia is crucial not only for ensuring equity and diversity in translational research but also for studying the Asian AD endotype.[10,12,13] Asian patients with AD, including Korean, Japanese, and Chinese patients, were more likely to have activated T_H17 and reduced T_H1 axes compared to those with European ancestry.[10–13,29]

In this study, we used the Olink CVD II panel, which consists of 92 proteins with a known or possible association with CVD, to characterize blood proteomics in 39 moderate-to-severe AD patients in Korea and 39 healthy volunteers. The Olink platform utilizes PEA technology, a highly specific and efficient high-throughput technique.[30,31]

To the best of our knowledge, this has been the most extensive AD proteomics study conducted in Asia, including Korea, Japan, and China. We showed that CVD-associated proteins in the circulation of the AD patients' profiles are distinct from those of healthy volunteers. The results suggest that this blood proteomic signature may potentially aid in detecting the risk and early diagnosis of CVD in AD patients. However, the utility of blood proteomics throughout the entire course of the disease remains unclear. For a comprehensive blood proteomic analysis, it is warranted to characterize both patients with acute and chronic AD.

The results of this study corroborate with most of the previous findings.[15–20,27,32] Proteins such as MMP12, CCL17, and IL16 were upregulated in AD patients. The concentration of CCL17 was strongly correlated with the disease severity score ($R = 0.543$). Furthermore, our findings demonstrated that the addition of FGF21 alongside CCL17 enhanced the R-value ($R = 0.619$) for multiple linear regression. FGF21 has been previously reported to be upregulated in AD patients.[27] A recent report suggested that the serum level of FGF21 significantly correlated with disease severity in European American patients with AD.[17]

The upregulated proteins reported in this study have been implicated in various CVDs. For example, CCL17 has been reported to aggravate myocardial injury in mouse myocardial infarction (MI) models.[33] Moreover, a multiprotein model for prognostic stratification integrating MMP12 outperformed the refit Framingham secondary

risk score in predicting future cardiovascular events.[34] IL16 is found in atherosclerotic plaques but may have a plaque-stabilizing impact, protecting against atherosclerosis and lowering clinical complications.[14]

Twenty-five proteins were found to be strongly correlated with each other. All correlating proteins were upregulated in AD. Since they correlated with each other while being upregulated in AD, we hypothesized that the 25 proteins could potentially serve as CVD-specific biomarker candidates for AD. Indeed, most of the candidate proteins have been mentioned in the literature and were noted to be associated with AD. The 22 previously reported proteins are as follows: CD84, CD40L, ANGPT1, PDGF subunit B, PARP1, GLO1, SRC, NEMO, TNFRSF10A, PAR1, PRSS27, Gal9, IL18, CCL17, MMP12, IL1RA, IL16, PTX3, LOX1, CEACAM8, TGM2, and Dkk1.[15–20,27,35–44]

To the best of our knowledge, STK4, ITGB1BP2, and DECR1 have not been mentioned in the context of adult AD patients. These three proteins were upregulated in our AD cohort and highly correlated with the other candidate proteins found in the literature (Fig. 4A and C), suggesting that they could comprise the characteristic findings of AD patients in Korea. *STK4* stands for serine threonine-protein kinase 4, and its mutation has been reported in patients with *DOCK8* deficiency-like condition.[45,46] STK4 deficiency results in progressive immunodeficiency in affected individuals and is often accompanied by mild AD-like dermatitis.[45] In our study, STK4 levels were significantly increased in AD. Thus, STK4 dysregulation may be associated with AD-like dermatitis. In relation to CVDs, STK4 deficiency conferred protection in murine MI models.[47] However, structural cardiac anomalies have also been observed in STK4-deficient patients.[45] Nonetheless, the role of STK4 in the context of CVD associated with AD has not been reported.

ITGB1BP2, also known as melusin, aids protein folding in cardiac and skeletal muscles. Its expression in the heart is upregulated in response to pressure overload,[48] and it has been shown to prevent the transition towards heart failure upon chronic pressure overload.[49] It increases upon ischemic injury and has a protective role in ischemia-reperfusion injury.[50,51] It was decreased in chronic aortic stenosis and postoperative atrial fibrillation patients.[52,53] While a few genetic variations in ITGB1BP2 have been reported in dilated and hypertrophic cardiomyopathies, their direct associations with these diseases remain elusive.[54,55] DECR1 is an auxiliary enzyme of the unsaturated fat metabolism pathway and functions to balance saturated and unsaturated phospholipids.[56] DECR1 expression level was negatively correlated with the disease severity score in pediatric AD patients (cohort age of 1.8 ± 1.6 years).[27] In contrast, DECR1 levels were elevated in the adult patients of Korea in this study.

Previous studies have noted that pediatric and Asian AD endotypes exhibit significant T_H17/IL23 activation and may share a common inflammatory pathway.[10] It is unknown whether DECR1 plays a role in the common pathway or contributes to pediatric and Asian AD pathogenesis. With reference to CVD, DECR1 elevation has been noted in individuals who have experienced MI.[56] In summary, the roles of STK4, ITGB1BP2, and DECR1 in AD pathogenesis and CVD development in patients with moderate-to-severe AD remain uncertain and warrant future investigations.

Pathway enrichment analysis of 25 highly correlated proteins from the CVD II panel indicated potential links between cardiovascular risks and AD, as enrichment was shown in vascular system involvement, inflammation, and lipid metabolism (Fig. 5). However, further research is required to establish causality and confirm their role in AD. Nonetheless, this study extends existing evidence on the AD-CVD association. Pathway analyses were conducted using a subset of 25 preselected proteins as potential CVD biomarkers, which may introduce selection bias. Performing pathway analyses with the complete set of 92 proteins or considering adding other CVD panels could help mitigate this potential bias.

This study has several limitations. It has a relatively small sample size; only 39 AD and 39 healthy volunteers were involved in this study. In addition, we only measured the expression levels of 92 proteins and acquired blood samples from a single time point. Expanding the number of proteins analyzed and acquiring data from multiple time points in a larger cohort is warranted to provide

more insights into AD proteomics and its association with CVD. In addition, AD patients and healthy volunteers who participated in this study had limited or unknown clinical histories of CVD. Selective recruitment of AD patients with known cardiovascular diseases could have elucidated distinctive CVD-associated proteomic profiles specific to AD.

CONCLUSION

The blood proteomics of moderate-to-severe AD in Korea were evidently distinguished from those of healthy volunteers with the CVD II panel. Furthermore, we have identified 3 unique proteins (STK4, ITGB1BP2, and DECR1) upregulated in this study cohort with their potential biological functions in AD and CVD. Significantly enriched pathways of the 25 highly correlated proteins of the CVD II panel were involved in the vascular system, inflammatory processes, and lipid metabolism.

Abbreviations

AD, Atopic dermatitis; CVDs, Cardiovascular diseases; CCL17, C–C motif chemokine ligand 17; DAVID, Database annotation, visualization, and integrated discovery; DECR1, 2,4-Dienoyl-CoA Reductase 1; DOCK8, Dedicator of cytokinesis 8; EASI, Eczema area and severity index; FGF21, Fibroblast growth factor 21; GO, Gene ontology; HC, Healthy control; ITGB1BP2, Integrin beta 1 binding protein 2; IL-6, Interleukin 6; MMP12, Matrix metallopeptidase 12; MI, Myocardial infarction; PCA, Principal component analysis; PEA, Proximity extension assay; qPCR, Quantitative polymerase chain reaction; STK4, Serine/threonine-protein kinase 4.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization: HJK and DHL. Data curation: HSK, JHM. Formal analysis: SPJ, HSK, JHM. Funding acquisition: HJK and DHL. Methodology: YKC, SKS, HJN, YJB, JSL, JEK, CGP. Writing – original draft: SPJ, HSK, JHM. Writing – review & editing: CGP, HJK, DHL.

Ethics approval and consent to participate

The study design was approved by the Seoul National University Hospital Institutional Review Board (H-1908-031-1052) and the Catholic University of Korea Eunpyeong St. Mary's Hospital Institutional Review Board (PC22SISI0076) before the study's commencement, according to the Declaration of Helsinki. All subjects provided written informed consent.

Declaration of competing interest

The authors declare that they have no competing interests.

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Author details

[a]Department of Dermatology, Seoul National University Hospital, Republic of Korea. [b]Department of Dermatology, Seoul National University College of Medicine, Republic of Korea. [c]Institute of Human-Environmental Interface Biology, Medical Research Center, Seoul National University, Republic of Korea. [d]Translational Medicine Major, Department of Medicine, Seoul National University College of Medicine, Republic of Korea. [e]Samsung Genome Institute, Samsung Medical Center, Seoul, Republic of Korea. [f]Human Immune Monitoring Center, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [g]Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, Republic of Korea. [h]Department of Dermatology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Republic of Korea. [i]Department of Microbiology and Immunology, Seoul National University College of Medicine, Republic of Korea. [j]Seoul National University Hospital, Seoul, Republic of Korea.

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