Shared Inflammatory Signatures Between Kidney and Skin in Chronic Kidney Disease: A Transcriptomic and Pathway-Based Approach

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Abstract:

Chronic kidney disease is a progressive condition with systemic effects, including dermatological manifestations such as pruritus and psoriasis. Transcriptomic analysis of the kidney and skin was analyzed in this study to uncover shared molecular mechanisms contributing to this link. Using RNA-Seq data from the Human Protein Atlas and Uppsala Biobank, this study identified over 10,000 differentially expressed genes and performed functional enrichment using Enrichr and STRING in Cytoscape. Arachidonic acid metabolism emerged as a key pathway enriched in both tissues, involving genes like CYP2C, CYP4A11(kidney), and ALOX12, CYP2C19(skin). These genes are involved in leukotriene and prostaglandin biosynthesis, which mediate inflammation. Disease enrichment analysis linked psoriasis genes to CKD (adjusted p-value = 4.047e-7), supporting a shared inflammatory axis. My findings suggest that dysregulation of the arachidonic acid metabolism pathway may underlie CKD-related skin symptoms and provide targets for future therapeutic interventions

Introduction:

Chronic Kidney Disease (CKD) affects between 8% and 16% of the global population. It can be caused mainly by kidney damage or decreased kidney function beyond the period of 3 months or more and is mainly known for its effects on renal filtration and metabolic regulation. Nevertheless, CKD is increasingly known with a wide range of secondary complications, which include cardiovascular, neurological, and dermatological manifestations. Among these, some of the non-specific manifestations include skin-related issues such as pruritus, dryness and inflammatory skin diseases such as psoriasis are particularly common but are frequently overlooked in clinical evaluations (Vivek Goel, et al. 2021).

Kidney plays a central role in different pathways, which include blood pressure regulation, waste removal, and metabolic homeostasis. On the other hand, skin serves as a protective barrier and as an immune interface with the external environment. Though these two tissues show distinct physiological roles and are not functionally identical, they share some similarities in cellular architecture, barrier function, and alertness to inflammatory signals. Therefore, disruptions in one organ system can have a cascading effect on others, increasing the chance/possibility of systematic crosstalk through shared systemic or metabolic pathways. One such potential shared link between these two tissues is the arachidonic acid metabolism pathway, which is mainly involved in producing eicosanoids, which are chemical messengers made from fat, especially from a fatty acid called arachidonic acid, and plays a key role in regulating inflammation, immunity, and other psychological responses. Dysregulation of this pathway has shown an impact in both renal pathologies and inflammatory skin conditions (J Cell Sci. et. al., 2012), Lennartz M, et al. (2023). Altered arachidonic acid metabolism in chronic kidney disease (CKD) may contribute to kidney damage as well as inflammation, possibly affecting distant tissues like the skin.

This project aims to look at transcriptomic profiles from kidney and skin tissues to identify shared pathways and genes that can explain how CKD contributes to skin-related symptoms. Using RNA-Seq data, differential expression analysis, and functional enrichment through STRING and Enrichr. I particularly focused on arachidonic acid metabolism as a pathway linking the renal and dermatological outcomes. By incorporating the gene expression data with disease associations and literature validation, I explored how molecular dysregulation in CKD may propel systemic inflammation and affect skin health.

Materials and Methods:

⇒ **Sample Source:**

RNA-Seq data from 3 kidney and 3 skin tissue samples, which are originally reported in the Human Protein Atlas and sourced from a study published in Science (PMID: 25613900). These were samples of human tissue collected

and handled by Swedish laws and regulations, and are obtained from the Department of Pathology, Uppsala University Hospital, Sweden, as part of the Uppsala Biobank. All the tissue samples were faceless and are represented as normal tissues, which is confirmed by pathologist review and ethical approval from the Uppsala Ethical Review Board (Reference # 2002-577, 2005-338, and 2007-159 (protein) and # 2011-473 (RNA)).

⇒ **Preprocessing:**

Quality assessment was performed using FastQC (v0.11.9), which identified high sequence quality for maximum reads but showed a slight degradation at the 3' end and very little adapter contamination. To overcome these issues, trimming was performed using Trim Galore (v0.0.6) by removing low-quality bases ($Q < 30$) and removing the reads whose length is shorter than 50bp. Quality check was performed post trimming and saw an improvement in read quality, with adapters removed successfully, ensuring perfect data for further downstream analysis.

⇒ **Mapping and Alignment:**

Clean reads were aligned to the GRCh38 reference genome using HISAT2 (v2.2.1), with up to 32GB of memory and 16 CPU cores per sample. The alignment process yielded high mapping rates across all samples, with kidney samples exceeding 98% and skin samples achieving nearly 93%. The alignment reads were stored in BAM files and were further sorted and indexed using SAM tools, enabling access for subsequent analysis.

⇒ **Read Counting:**

Read counts were calculated using **HTSeq-count** (v 2.0.1) to generate gene level counts. Counts were saved in .txt format and then merged on later in R for analysis. This step produces count matrix that is essential for differential expression analysis and normalization.

⇒ **Normalization and Differential expression:**

edgeR (v3.36.0), package specifically designed for RNA-Seq data was used for normalization and differential expression analysis. Normalization was conducted in-order to adjust the library size across all samples. Genes with an adjust P-value (FDR) < 0.05 were considered differential expressed. This analysis identified 10,043 genes differentially expressed genes, showing a distinct expression patterns between kidney and skin.

⇒ **Enrichment and Network Analysis:**

Significant genes were analyzed using Enrichr(MaayanLab v2025) for pathway and functional enrichment. Biological processes and KEGG 2021 Human pathways like Arachidonic acid metabolism were highlighted. Protein-protein interaction networks networks were constructed using the STRING (v2.2.0) database highlighting tissue specific genes.

⇒ **Visualization Tools:**

R (v4.4.2) was used for generating multiple exploratory visualizations, including the Biological Coefficient of Variation (BCV) plot, smear plot, PCA, MDS and hierarchical sample clustering heatmap. Heatmaps displayed clustering of top 50 differentially expressed genes, illustrating tissue specific expression profiles. Whereas PCA and MDS plots showed a clear separation of replicates based on tissue type.C

Results:

1. Quality Assessment and Preprocessing:

Sample	Tissue	Total reads processed	Reads with Adapters	% reads removed for low quality	% of reads filtered out due to short length
Kidney_a	Kidney	20,000,000	6,097,307	14.6%	12.0%
Kidney_b	kidney	20,000,000	7,697,060	14.1%	11.4%
Kidney_c	Kidney	20,000,000	4,938,015	14.5%	12.3%
Skin_5e	Skin	20,000,000	7,117,023	3.70%	4.10%
Skin_5f	Skin	20,000,000	7,144,362	3.60%	3.70%
Skin_6a	Skin	20,000,000	8,001,212	3.60%	3.90%

Table-1: *Summary of key quality control metrics from the raw RNA -Seq data for all kidney and skin samples*

2. Alignment:

Reads were aligned to the GRCh38 human reference genome using **HISAT2**. The alignment rates across all six samples were high, with kidney samples showing alignment rates greater than 98% and skin samples exceeding 93%. These high mapping rates indicate good sequence quality and suggest that the reads were accurately aligned to the reference genome, ensuring reliable results and are stored in sorted BAM files for downstream transcriptomic analysis.

3. Differential Expression Analysis:

Gene	Tissue	LogFC	FDR
UMOD	Kidney	-18.6912436838749	1.9540499068573E-145
KRT1	Skin	19.3446875290539	9.59207175970543E-131
SBSN	Skin	17.9585630661417	1.56448645499236E-114
CDH16	Kidney	-16.2925251214685	4.39268555576218E-114
KNG1	Kidney	-14.2824377200929	1.06297024147699E-106
TMEM213	kidney	-11.5522646361549	9.38839474445433E-104
KRT14	Skin	15.1406411898402	1.10324331050523E-103
KCNJ16	Kidney	-11.3765687727717	4.07961652614474E-103
SERPINA12	Skin	15.0029196805641	2.54445088085882E-101
CCDC198	Kidney	-13.8436639252452	1.86831227818326E-99

Table-2*: Top differentially expressed genes identified between skin and kidney samples. Genes are classified based on LogFc values, with corresponding FDR indicating statistical significance.*

Using DESeq2, a total of 10,043 genes were identified as differentially expressed between kidney and skin tissues based on an adjusted p-value threshold of < 0.05 and a $|\log2 \text{ fold change}| > 1$. Among these, 4,670 genes were found to be significantly upregulated in skin, while 5,373 genes were significantly upregulated in kidney. This clear division highlights the distinct transcriptomic profiles of these tissues and guided further enrichment analysis on the top 50 upregulated genes from each group.

4. Exploratory Analysis:

Exploratory data analysis was conducted to evaluate variability, quality, and relationships between samples prior to downstream analysis. This step is essential for assessing consistency between biological replicates, identifying outliers, and visualizing patterns in gene expression across conditions.

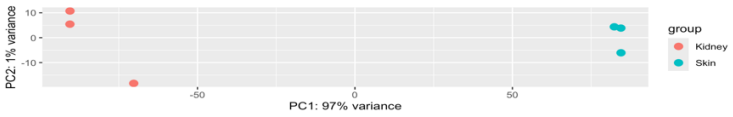

Figure 1: Principal Component Analysis plot for Tissue Clustering

Principal Component Analysis revealed clear separation between kidney and skin samples. PC1 accounted for 97% of the total variance. Kidney samples clustered tightly on one side of the plot, while skin samples formed a distinct group on the opposite end

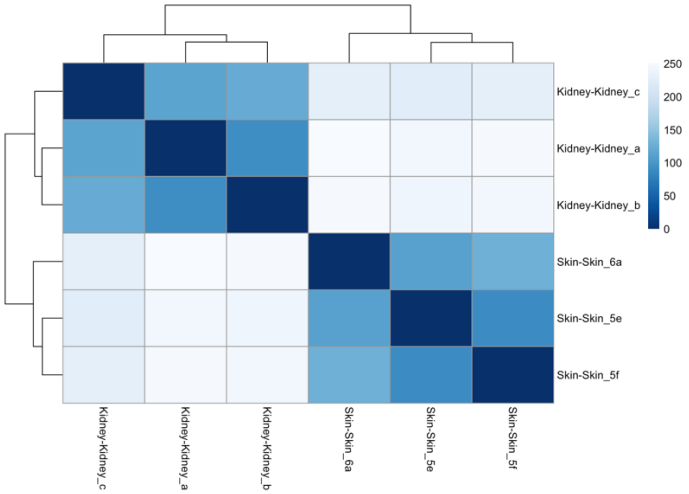

Figure 2: Correlation heatmap for Kidney and small intestine

Displays pairwise correlation coefficients between all samples. The heatmap shows strong intra-group correlations among kidney samples and among skin samples. The clear distinction between tissue types supports the separation observed in PCA and clustering plots.

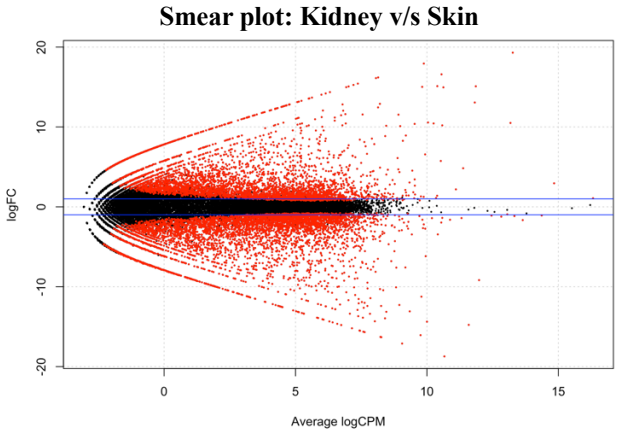

Figure 3: Smear plot of Differential Expression Analysis (Exact Test)

Displays LogFC distribution of genes between kidney and skin. Red dots indicate the differentially expressed genes.

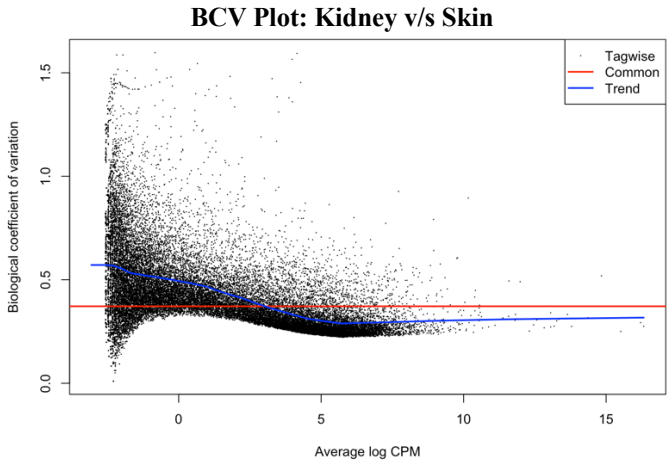

Figure 4: Biological co-efficient variation plot (BCV) for Kidney and skin

The BCV plot showed disruption of biological variation across all expressed genes. Most genes clustered around a dispersion value of 0.2, which is expected in well-controlled RNA-Seq data. The stability in dispersion indicates consistent variability and reliable biological signal between replicates.

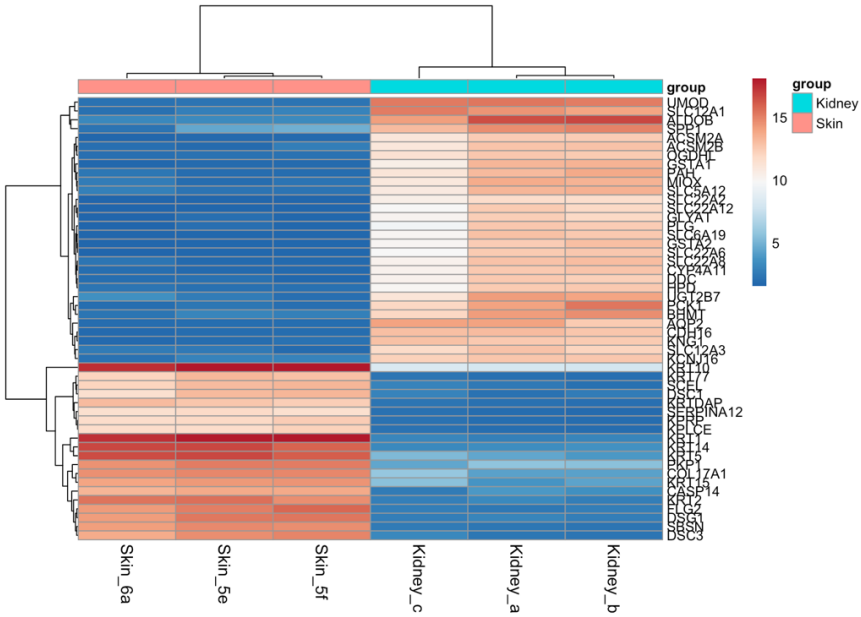

Figure 5: Heatmap of top differentially expressed genes

The hierarchical clustering heatmap clearly separated kidney and skin samples into two distinct clusters, demonstrating strong tissue-specific gene expression and high sample consistency.

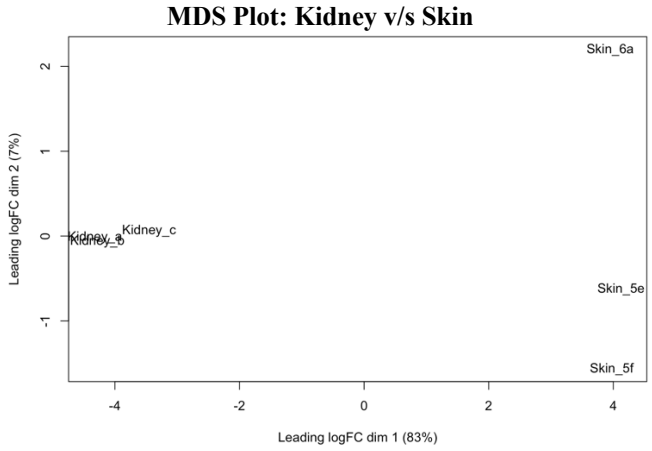

Figure 6: Multidimensional Scaling plot

Multidimensional Scaling based on logFC distances further validated the separation of kidney and skin groups, reinforcing sample consistency and expression divergence between tissues.

5. Functional Enrichment via Cytoscape and Enrichr:

To uncover the biological significance of top differentially expressed genes, functional enrichment analysis was conducted using Enrichr and visualized the protein-protein interactions in top 50 differentially expressed gens in both Kidney and Skin.

⇒ Kidney Enrichment:

The top 50 differentially expressed genes were the input for Enrichr platform in-order to identify significantly enriched Gene Ontology (GO) biological processes and pathways. The results revealed a strong enrichment for kidney related functions including ion-transport, renal magnesium handling, and water reabsorption process. KEGG pathway analysis also highlighted Aldosterone regulated sodium reabsorption and mineral absorption, which are closely tied to renal physiology.

Protein-protein interaction (PPI) analysis (*Figure -7*) was then performed using STRING within Cytoscape. The resulting network showed dense interconnectivity among key renal function regulators, including SLC family transporters and AQP2, forming a central hub within the idney expression cluster.

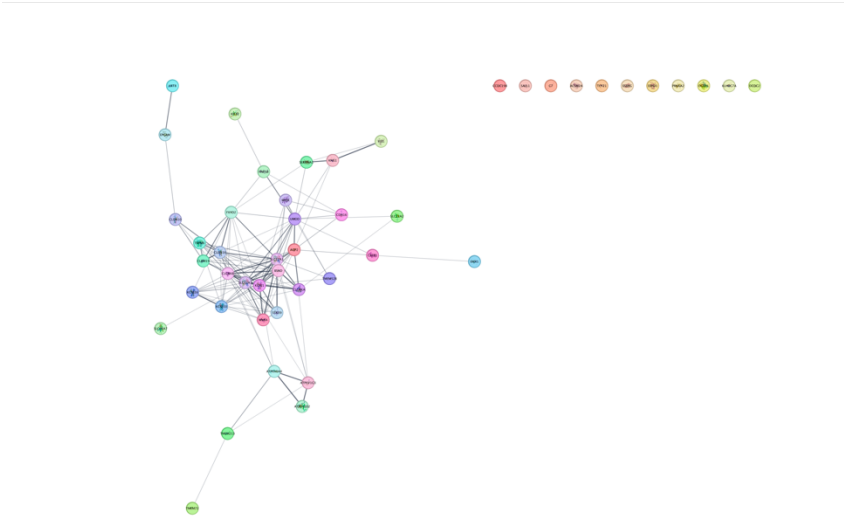

Figure 7: Protein-protein interaction network of top – 50 kidney upregulated genes

Visualizes protein interactions among top 50 upregulated kidney genes. Key renal transport genes like AQP2 and SLC family members form central hubs which are linked to CKD.

⇒ **Skin Enrichment:**

Similarly, the top 50 upregulated genes from skin tissue were analyzed in Enrichr. GO enrichment showed dominant terms such as keratinization, epidermal development and formation of the cornified envelope. KEGG pathway results included ECM-receptor interaction and cytokine-cytokine receptor interaction. Which actively participate in roles such as skin barrier function and immune signaling.

String network analysis (Figure – 7) showed a strong interconnection between keratin and involucrin genes (e.g., KRT1, KRT14, IVL, DSC3), which strongly supports skin differentiation

and barrier integrity. These proteins formed tightly knit clusters, indicating co-expression and likely co-functionality within the epidermal architecture.

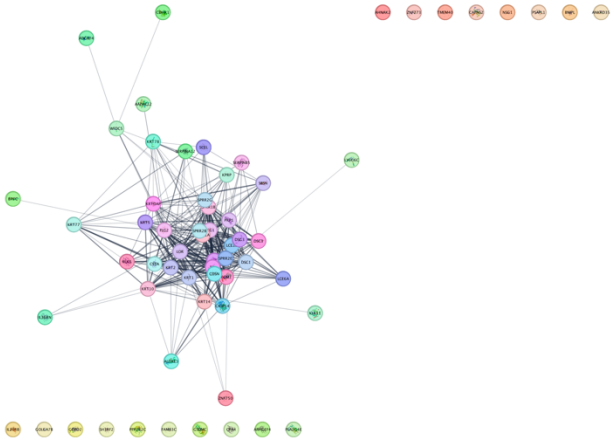

Figure – 7: Protein-protein interaction network of top 50 upregulated skin genes.

String network depicting central nodes including keratin related proteins such as KRT1 and DC3, highlighting roles in skin structure and inflammation.

Interestingly, in both kidney and skin enrichment analysis, the arachidonic acid metabolism pathway was identified as significantly enriched through KEGG. This is one of the crucial pathways playing a central role in synthesis of pro-inflammatory mediators such as prostaglandins and leukotrienes., which are implicated in both renal inflammation and skin disorders such as psoriasis. The overlap was further supported by the presence of distinct genes in each tissue involved in this pathway.

Gene	Tissue	Role
CYP2C	Kidney	Inflammatory mediated synthesis downregulated in CKD
CYP4A11	Kidney	Eicosanoid synthesis, linked to vascular function in CKD
CYP2C19	Skin	Involved in drug metabolism, inflammation regulation (Roy O. Mathew et. al.,2022)
ALOX12	Skin	Promotes Leukotriene biosynthesis, elevated in diabetic kidney disease. (Meixi Wang et. al.,2024)
PTGS	Skin	Catalyzes prostaglandin formation, involved in skin inflammation

Table 4: Enriched arachidonic acid metabolism by tissue

This common enrichment highlights arachidonic acid metabolism as a potential systematic inflammatory mechanism bridging kidney dysfunction and skin inflammation and also demonstrates how different genes contribute to this shared pathway supporting tissue-specific inflammation with systematic origin.

⇒ **KEGG pathway map** (Figure – 8):

Visualized gene locations in arachidonic acid metabolism highlighting CYP and ALOX family genes (Bei Wang et. al., 2021) involved in both kidney and skin function. These genes are centrally positioned within the pathway and contribute to the synthesis of pro-inflammatory molecules such as prostaglandins and leukotrienes. Their expression both tissues underscore the relevance of this pathway in mediating systemic inflammation associated with CKD.

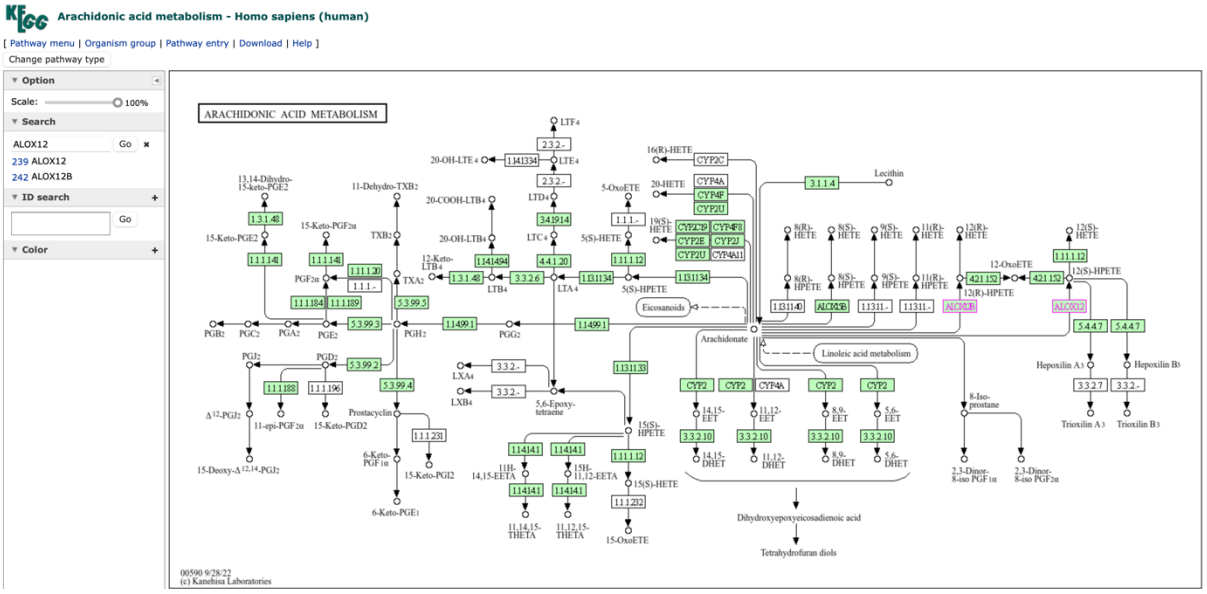

Figure – 8 : KEGG Arachidonic acid pathway

This figure highlights the involvement of key inflammation-related genes across both kidney and skin tissues. Kidney – enriched genes like CYP2C and CYP4A11, and skin associated genes such as CYP2C19, ALOX12 and PTGS are all mapped within the pathway. Pink highlighted nodes such as ALOX12 indicate genes which are highly active in Leukotriene biosynthesis – a major driver of inflammatory conditions like psoriasis and diabetic kidney diseases.

⇒ Disease Link – Psoriasis and CKD

In-order to further validate the biological relevance of these findings, psoriasis – associated genes ere analyzed using Enrichr and cross – referenced against disease associations in DisGeNET. The analysis revealed a significant association between these genes and chronic kidney disease (**adjusted p-value = 4.047e-7**). This strong connection indicates that a molecular overlap in inflammatory mechanisms between CKD and skin disorders such as psoriasis. The enriched arachidonic acid metabolism genes identified in both tissues may represent shared molecular mediators contributing to the inflammatory crosstalk between kidney dysfunction and skin pathology.

6. Discussion:

This study uncovers a molecular link between kidney dysfunction and skin inflammation through transcriptomic profiling of healthy human kidney and skin tissue. My multi-step approach combined RNA-Seq differential expression analysis with network and enrichment-based interpretation to propose a shared inflammatory axis- arachidonic acid metabolism between two human tissues.

The enrichment of this pathway in both kidney and skin was supported using Enrichr and STRING. Specifically, I identified CYP2C and CYP4A11 as kidney–specific genes within the supporting materials, mentioning that reduced CYP2C activity can alter eicosanoid signaling in CKD patients(Thomas J. Velenosi et. al., 2012, M A Suarez-Santisteban et. al., 2024). On the other hand, in skin genes such as CYP2C19, ALOX12, and PTGS were involved and are linked to inflammatory dermatoses like psoriasis. ALOX12 is shown to be elevated in diabetic kidney disease and plays a major role in leukotriene biosynthesis.

The string-based protein-protein interaction (PPI) networks (Figures 6 and 7) provided a clear systems-level view of how these tissue-specific genes cluster functionally. Kidney genes were mainly involved in solute transport (AQP2, SLCs), while skin mainly revolved around keratinocyte integrity (KRT1, IVL, DSC3), which strongly demonstrates organ-specific expression but is united by a common inflammatory signature.

A key insight emerged from the disease Enrichment analysis using DisGeNET, where psoriasis gene signatures showed significant overlap with CKD (adjusted-p = 4.047e-7). This finding strongly builds a strong functional bridge between skin manifestations in CKD patients and renal-originated inflammation, particularly through arachidonic acid metabolism.

The KEGG pathway map (Figure 8) had visually supported our molecular claims by locating all identified genes within the cascade of leukotriene and prostaglandin biosynthesis. The pink highlighted ALOX12, mapped alongside CYP enzymes, emphasized its central role in inflammatory mediator production.

Overall, these results affirm the hypothesis that CKD-related systemic inflammation can manifest in peripheral organs such as the skin. This suggests that arachidonic acid metabolism is not only responsible for the shared molecular target but also serves as a potential therapeutic axis for CKD-associated coexisting conditions. DisGeNET enrichment connecting psoriasis genes with CKD further supports this hypothesis. By revealing specific shared genes and processes, my results contribute to understanding the molecular basis of skin symptoms in CKD patients and highlight the potential for targeting inflammatory pathways across tissues.

7. Future Directions:

- Increasing the number of biological replicates and incorporating patient-clinical metadata (e.g. CKD stage, skin condition severity) will enhance the statistical power and clinical relevance f the findings.
- Applying single-cell RNA sequencing could identify specific cell types driving arachidonic acid metabolism alterations in kidney and skin. (Jie Cheng, Hang Wang et. al. 2024)
- Computational screening could be used to identify drugs that modulate arachidonic acid metabolism, offering a potential strategy to mitigate both renal and dermatological inflammation in CKD patients.

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