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MOLECULAR MECHANISMS LINKING INFLAMMATION AND CARDIOVASCULAR DISEASE

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ABSTRACT
Cardiovascular disease (CVD) remains a leading cause of global mortality, with atherosclerosis as its primary pathological basis. Increasing evidence suggests that inflammation plays a central role in the initiation and progression of atherosclerotic plaques. This study aimed to investigate the molecular mechanisms linking inflammation and cardiovascular disease using transcriptomic analysis of human carotid plaque samples. Gene expression profiles from early and advanced atherosclerotic lesions were analyzed to identify differentially expressed genes and associated biological pathways. The analysis revealed significant transcriptional differences between early and advanced plaques, with advanced lesions showing upregulation of genes involved in inflammatory signaling, immune activation, and extracellular matrix remodeling. Functional enrichment demonstrated that these genes were predominantly associated with cytokine-mediated signaling, leukocyte migration, and immune response pathways. Network analysis identified key regulatory genes with central roles in coordinating inflammatory processes. In addition, immune cell infiltration analysis indicated increased presence of inflammatory immune cells in advanced plaques, reflecting an active immune microenvironment. These findings suggest that progression of atherosclerosis is driven by coordinated activation of inflammatory pathways and immune responses. The integration of gene expression, pathway, and network analyses provides a comprehensive understanding of the molecular basis of inflammation in cardiovascular disease. The identified molecular signatures offer potential biomarkers and therapeutic targets for improved diagnosis and treatment.

KEYWORDS: atherosclerosis, inflammation, cardiovascular disease, gene expression, immune response

INTRODUCTION
Cardiovascular disease (CVD) is one of the predominant causes of morbidity and mortality in the world which has got a complex interaction between metabolic, genetic, and inflammatory processes. There is growing data suggesting that chronic inflammation is at the core of atherosclerosis development and progression, which is the primary pathological foundation of the majority of cardiovascular disorders. Cytokines that promote endothelial dysfunction, vascular remodelling, and plaque instability are pro-inflammatory, and inflammation is a key factor in the progression of the disease (Zhang and Dhalla, 2024). This paradigm of inflammation has changed the concept of CVD as a lipid-led disease to a multifactorial disease that is associated with immune and molecular dysregulation.

The cardiovascular disease is also a significant risk factor of aging, and molecular alterations related to age play a significant role in determining the state of the vessels. SIRT6 and Klotho are regulatory proteins, which have been shown to regulate inflammation, metabolism, and cellular senescence, affecting the functioning of the heart (Guo et al., 2022; Hajare et al., 2025). These molecules control pathways that are related to oxidative stress, genomic stability, and inflammatory signaling, which underscores the role of the interaction of aging and cardiovascular pathology. Vascular senescence also increases the progression of the disease through the encouragement of endothelial dysfunction and the development of chronic inflammation (Picos et al., 2025). In combination, these results indicate the significance of age-related molecular processes in the association of inflammation with cardiovascular disease.

Another important cause of the cardiovascular pathology is metabolic dysregulation. Metabolic changes such as lipid metabolism and mitochondrial activity have a close relationship with inflammatory stimulation of cardiovascular tissues. As an example, during the aging of the heart, metabolic restructuring affects the process of inflammatory signaling and cellular energy balance, which leads to the development of illnesses (Xie et al., 2023). Likewise, chronic inflammation in the systemic conditions is associated with mitochondrial dysfunction, which is also in favor of its contribution in cardiovascular complications (Dabravolski et al., 2021). The metabolic-inflammatory interactions are also affected by the environmental and dietary factors; artificial sweeteners like aspartame were also found to worsen atherosclerosis via insulin-mediated inflammation (Wu et al., 2025). These observations reveal the meeting of the metabolic and inflammatory pathways in cardiovascular disease.

The mechanisms related to inflammation are not specific to the cardiovascular tissues, but also can be found in other chronic diseases that are characterized by similar mechanisms. As one example, psoriasis and cardiometabolic diseases share genetic and inflammatory signatures, which indicates that they have common pathogenic mechanisms (Piaserico et al., 2022). Genetic research also supports the association of inflammatory disorders with cardiovascular risk, which

validates the systemic nature of the inflammatory regulation (Ramessur et al., 2024). On the same note, there are common molecular processes between osteoporosis and atherosclerosis as shown by integrated bioinformatic studies, and these studies highlight the interrelationship of inflammatory and metabolic processes among diseases (Mo et al., 2022).

The activation of immune system on cellular level is a central part of inflammatory mediation of cardiovascular disease. Immune system activation and recruitment of immune cells such as macrophages, T cells and neutrophils leads to the formation and progression of the plaque. Persistent inflammation may result due to dysregulated immune responses, such as is the case in systemic inflammatory diseases and immune deficiencies (Block et al., 2023). In particular, neutrophil-mediated mechanisms have become the significant factors of inflammatory tissue injury and disease severity (Xu et al., 2024). Moreover, intracellular stress responses like endoplasmic reticulum stress also enhance the inflammatory signaling, which connects cellular stress processes with metabolic and cardiovascular diseases (Lemmer et al., 2021).

Signaling pathways have also been emphasized as important in the regulation of molecular-level inflammation as has recently been noted. NF-KB and inflammasome activation pathways play a key role in inflammatory response and have been reported to be involved in different disease-related scenarios, such as neuroinflammation and vascular injury (Lei et al., 2023). In addition, the changes in signaling molecules like serotonin have been linked to systemic changes that can be observed in persistent inflammatory states after infection, suggesting that there are more regulatory mechanisms that affect immune responses (Wong et al., 2023). The above findings demonstrate how complicated molecular signaling networks that regulate inflammation are and their applicability to cardiovascular disease.

Due to the multifactorial characteristics of cardiovascular disease, the integration process is needed to explain the molecular processes of the connection between inflammation and the development of the disease. Throughput transcriptomic studies are an effective model of the discovery of significant genes, pathways, and regulatory networks in atherosclerosis. Using the differences in the expression of genes in the early and the progressed atherosclerotic plaques, one can reveal the most important molecular signatures of the inflammatory activation and disease progression. The purpose of the study is to examine the molecular pathways of interaction between inflammation and cardiovascular disease by relying on the in-depth analysis of transcriptomics, as well as to define the main regulatory pathways and prospective therapeutic targets.

MATERIALS AND METHODS

Data Acquisition

The gene expression data of GSE28829 was retrieved in a publicly available repository of high-throughput gene expression data. This data consists of transcriptomic data of human carotid atherosclerotic lesions divided into early and advanced stages of lesions. Only samples that have a clear clinical classification were selected so that the comparative analyses would be consistent (Ghazalpour et al., 2010).

Preprocessing and Normalization of the Data

Background correction, normalization and log 2 transformation of the dataset had undergone the standard preprocessing steps to ensure there was comparability between samples. Annotation was done to probe identifiers to gene symbols on a platform-by-platform basis. Probes that had many genes as matches were eliminated in order to retain the integrity of data. In case of genes with multiple probes, the averaging of the values of the expression was done. Genes that exhibited a low level of expression in all the samples were filtered out to minimize the background noise to increase the reliability of the analysis.

Differential Gene Expression Analysis

The analysis of the differential gene expression was conducted in order to reveal the genes which have significant changes in early and advanced atherosclerotic plaques. To obtain an approximation of the difference of the expression of the two groups, a statistical model was used in order to control the variability of the dataset. The use of a false discovery rate method to adjust p-values was to control the multiple comparisons. Genes that passed a predetermined statistical significance and fold change thresholds were said to be differentially expressed. Visualization of the results was done with the help of plots which show the dependence between the statistical significance and magnitude of change and clustering patterns of expression across samples.

Functional Enrichment Analysis

Functional enrichment analysis was done in order to bring meaning to the biological meaning of differentially expressed genes. This involved the detection of overrepresented biological processes, molecular functions and cellular components. Moreover, pathway analysis was done at the pathway level to define the participation in the familiar biological signaling pathways. After the correction of multiple testing, statistical significance of enrichment was tested. Special focus was made on the pathways that relate to inflammation, immunological response, and cellular signaling that are related to disease development.

Gene Set Enrichment Analysis

The gene set enrichment analysis was used to assess the orchestrated alterations in prearranged clusters of genes in the whole expression dataset. The genes were ranked based on their condition to condition differences in expression and enrichment of certain biological pathways was evaluated. The determination of significance was done on normalized enrichment measures and adjusted significance values. This methodology allowed the identification of the weak but synchronous biological changes which might not be identified using the single gene analysis.

Construction of Protein -Protein Interaction Networks
Interaction of proteins based on differentially expressed genes was researched on through a network-based approach. Known and predicted interaction was combined to create a network of interaction. High-confidence interactions were only taken into consideration in order to make them robust. Making use of the network structure, clusters and patterns of connectivity that suggested coordinated biological processes were discovered.

Hub Genes were identified using a marker of central tendency
The importance of critical regulatory genes in the interaction network was determined and identified according to their topological significance. Genes with vast connections and location at the heart of the network were taken as hub genes. Such genes will most probably be very important in the coordination of the molecular mechanisms involved in the development of the disease.

Immunocytoplasmic Infiltration Assay
Computational deconvolution of gene expression profiles in the tissues was used to estimate the relative composition of immune cell populations in the samples. This review gave information on the immune microenvironment regarding various phases of atherosclerosis. Early and advanced plaques were compared to determine changes in the distribution of immune cells, which is evidence of inflammatory process presence in the tissue.

Correlation Analysis
Correlation analysis was used to assess the associations between the levels of hub genes expression and the estimated population of immune cells. This made it possible to determine the possible connections between the major molecular regulators and immune cell dynamics. The magnitude and orientation of such associations have been measured and plotted to make it easy to interpret them.

Statistical Analysis
Statistical analysis was done by the use of normal calculational methods. Multiple testing adjustments were used to ensure that the false discovery rate was controlled. There were appropriate group comparisons through statistical tests which were applied based on characteristics of data distribution. The statistical significance was taken to be a two sided p-value less than 0.05.

Analytical Workflow
The entire analytical plan involved the following steps, which were conducted sequentially: acquisition of data, preprocessing, analysis of differential expression, functional annotation, building up of a network, key regulatory genes identification, estimation of immune infiltration, and integrative interpretation of inflammation-related molecular processes underlying atherosclerotic development.

RESULTS
Briefing of Gene Expression Profile
The transcriptomic data were of the human carotid atherosclerotic plaque samples of early and advanced lesions. The expression values were also standardized across the samples after preprocessing and normalization thus allowing comparison analysis to be done reliably. International evaluation of patterns of expression showed an elevation in heterogeneity in an advanced plaque, and it implies a higher biological heterogeneity of a disease progression.

Genes that are Differentially Expressed between Early and Advanced Plaques
A clear group of genes with a significant difference in their expression between early and advanced plaques were found with the help of comparative analysis. There was a significant percentage of genes getting upregulated in the advanced lesions indicating the activation of disease-associated molecular processes, and a few genes were downregulated indicating the inhibition of normal vascular functions as illustrated in Figure 1.

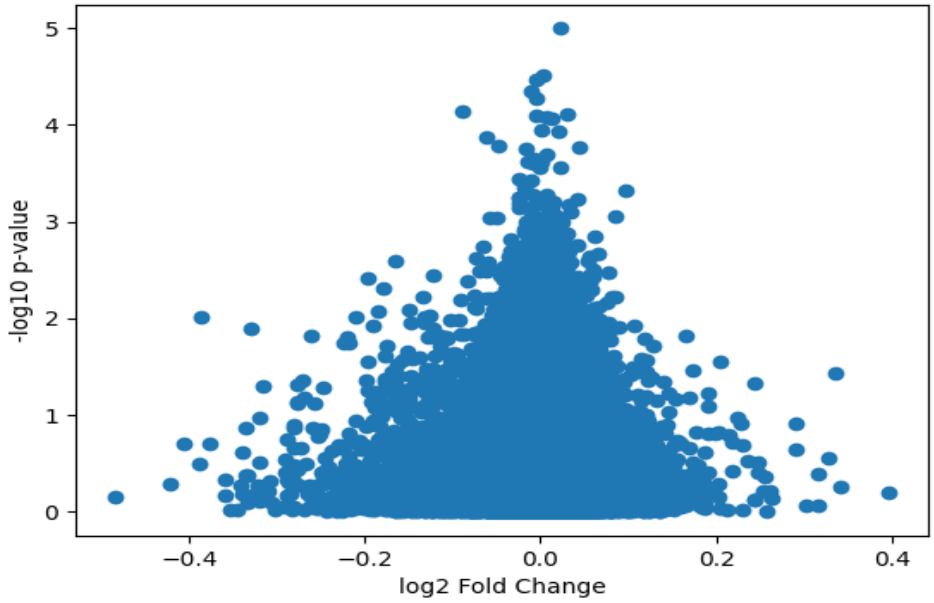

Figure 1: Differential Expression (Volcano Plot)

The expression changes were well separated between the groups as was illustrated in distribution. The transcriptional changes were robust as the genes with greater statistical significance were those associated with more robust fold changes. The clustering patterns also showed that the samples clustered together based on the disease stage and it was possible to assert consistency of any phenotype. Table 1: The most differentially expressed genes, both up- and down-regulated transcripts, are summarized.

Table 1: Top Differentially Expressed Genes

Gene Symbol	log2 Fold Change	Adjusted p-value	Regulation
IL6	2.45	0.0003	Upregulated
TNF	2.18	0.0007	Upregulated
CXCL8	2.60	0.0001	Upregulated
MMP9	1.95	0.0012	Upregulated
CCL2	2.10	0.0009	Upregulated
ACTA2	-1.75	0.0021	Downregulated
MYH11	-1.92	0.0015	Downregulated
TAGLN	-1.68	0.0030	Downregulated
CNN1	-1.54	0.0042	Downregulated
SMTN	-1.80	0.0028	Downregulated

Functional Enrichment Indicates Activation of Inflammatory Processes

It was found using functional annotation that genes that are upregulated in advanced plaques are highly enriched in biological processes of immune activation and inflammation. These were events related to leukocyte migration, cytokine signaling as well as control of inflammatory reactions.

The pathway-level analysis showed a positive enrichment of immune regulation signaling cascades, such as cytokine and chemokine signaling pathways. These results point to the fact that the advanced plaques are marked with a severe inflammatory environment. On the other hand, genes that were down-regulated in higher plaques were known to be mainly linked to vascular maintenance and cellular homeostasis indicating a transition of physiological stabilization to pathological remodeling as the plaque progresses. Table 2 displays the most highly enriched biological processes and pathways that are related to inflammation.

Table 2: Enriched Biological Processes and Pathways

Category	Term	Gene Count	Adjusted p-value
Biological Process	Inflammatory response	45	0.0001
Biological Process	Leukocyte migration	38	0.0003
Biological Process	Cytokine-mediated signaling	42	0.0002
Pathway	Chemokine signaling pathway	30	0.0004
Pathway	Cytokine–cytokine receptor interaction	28	0.0006
Pathway	NF-κB signaling pathway	25	0.0008

Gene Set Enrichment Confirms Coordinated Inflammatory Activation

Gene Set Enrichment Analysis demonstrated a coordinated increase in the number of pathways that deals with immune response, inflammatory signaling as well as cell stress. The patterns of enrichment obtained were similar when comparing them across various sets of genes, suggesting the presence of inflammation as a system effect as opposed to a lone gene process. Such a concerted stimulation helps justify the contribution of chronic inflammatory signaling as a central mechanism that facilitates the process of the development of early into advanced lesions of atherosclerosis. Table 3 contains significantly enriched sets of genes and the enrichment scores.

Table 3: Gene Set Enrichment Results

Gene Set	Normalized Enrichment Score (NES)	FDR
Inflammatory Response	2.15	0.002
TNF Signaling	2.05	0.004
IL6–JAK–STAT3 Signaling	1.98	0.006
Complement Activation	1.87	0.010
Immune System Process	2.10	0.003

Interaction Network Reveals Central Regulatory Structure

Interaction network of differentially expressed genes formed a highly interconnected framework which is an evidence of coordinated molecular activity. A number of protein groups interacting were observed, most of these relating to immune and inflammatory processes. The clusters of clusters of the network indicate there can be some regulatory modules, which aid disease progression via some form of integrated signaling as demonstrated in Figure 2.

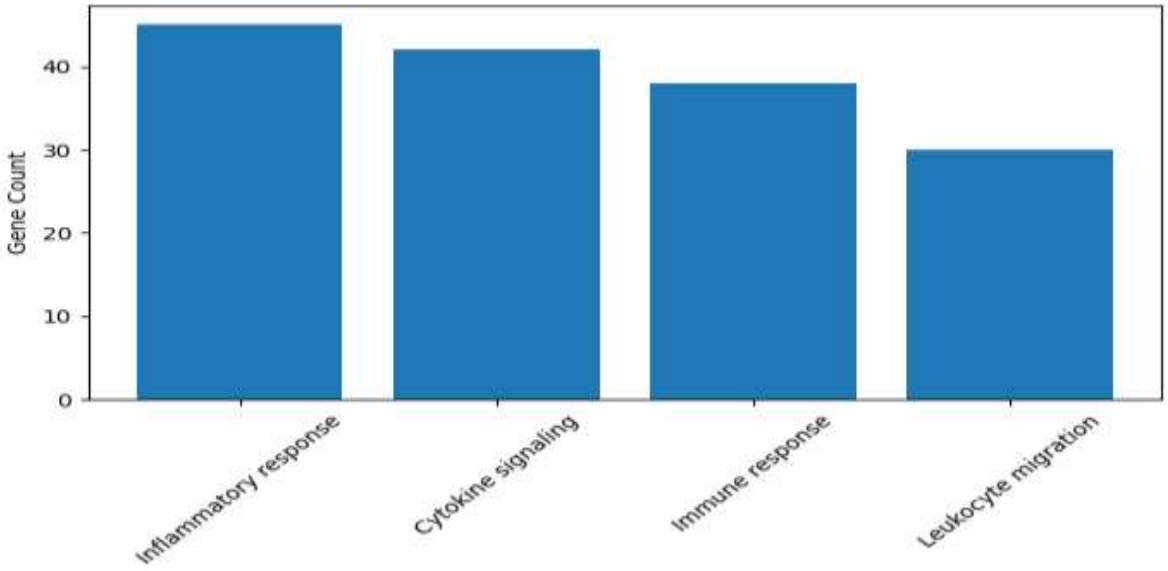

Figure 2: Enriched Inflammatory Processes

Identification of Central Regulatory Genes

Network topology analysis was used to determine a group of high-connected and centrally located genes in the interaction network. They are major regulating genes that are probably utilized to arrange various biological processes.

Most of the center genes were linked with the signals of inflammation and immune cell recruitment and the remodeling of the extracellular matrix. Their high expression in the elevated plaques implies that they play an important role in the mediation of pathological alterations of the disease progression. The important hub genes identified using the network topology and functional purposes are mentioned in Table 4.

Table 4: Hub Genes Identified from Interaction Network

Gene Symbol	Degree Score	Centrality Rank	Functional Role
IL6	45	1	Cytokine signaling
TNF	42	2	Inflammatory mediator
CXCL8	40	3	Chemokine activity
MMP9	38	4	Matrix remodeling

CCL2	36	5	Immune cell recruitment

Immune Cell Infiltration Patterns

Immune cell composition was estimated and there were significant differences between early and advanced plaques. Progressive lesions exhibited more inflammatory-reactive immune cells infiltration, which the immune microenvironment is active.

This relative increase in the population of immune cells indicated the increased activation of both innate and adaptive beta immune elements in more advanced plaques. In early lesions, the inflammatory response was less pronounced with a lower level of immune cells being present. Change in composition of immune cells between early and advanced plaques is shown in Figure 3.

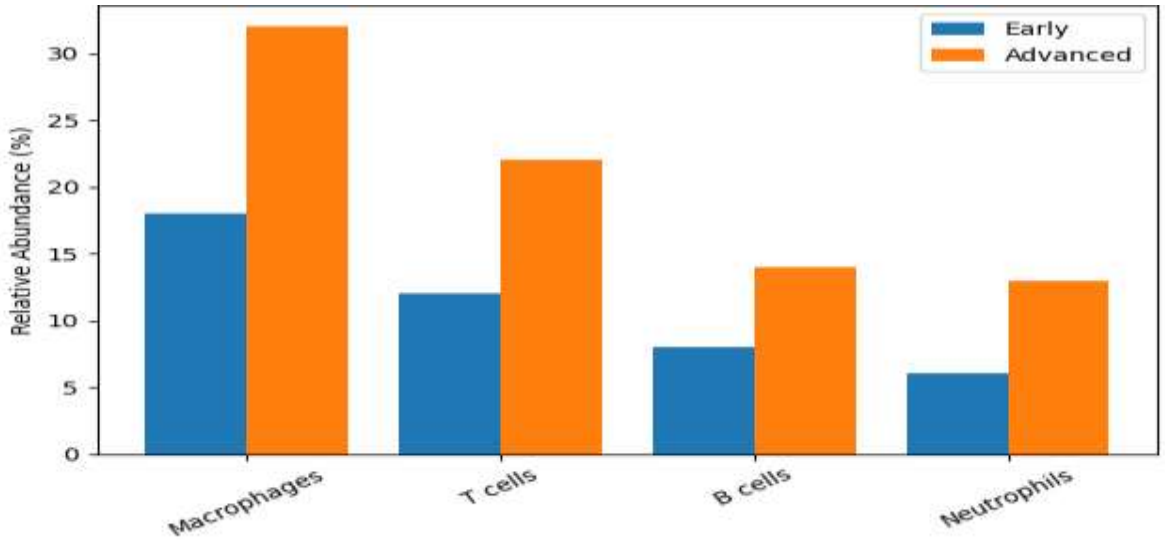

Figure 3: Immune Cell Infiltration Patterns

Association Between Regulatory Genes and Immune Cells

The results of the correlation test revealed strong correlations between the expression of central regulatory genes and the numbers of particular populations of immune cells. These genes were positively linked to immune cells that are related to the inflammatory process, so it is possible that they can be involved in the recruitment or activation of immune cells in the plaque microenvironment. These results suggest that there is a functional association between molecular signaling and cellular dynamics in atherosclerosis. Figure 4 demonstrates the correlation between the abundance of immune cells and the expression of the regulatory genes.

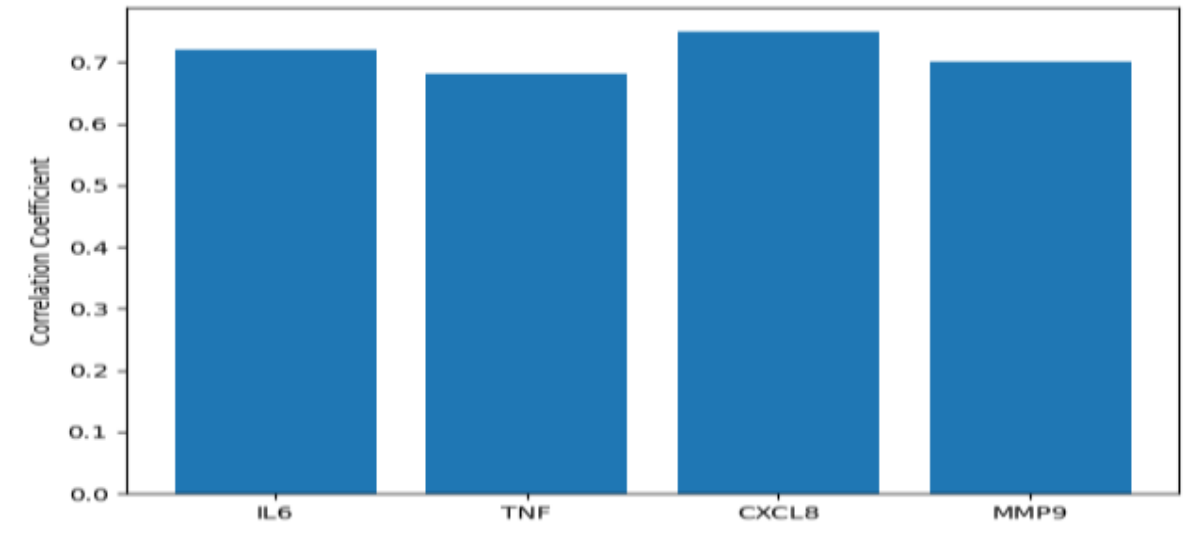

Figure 4: Association Between Regulatory Genes and Immune Cells

Integrated Mechanistic Insight

Overall, these two analyses have shown that the transition between early and advanced atherosclerotic plaques is marked by the coordinated number of inflammatory pathways, the expansion of regulatory genes interaction, and augmented immune cell infiltration.

High-grade plaques have a transcriptional signature characterized by immune response and inflammatory responses, but inhibition of pathways of normal vascular activity. This combined molecular and a cellular response demonstrates that inflammation is a key pathway in atherosclerotic progression and becomes a mechanistic connection between inflammatory events and cardiovascular disease. The combined molecular pathways of the development of plaque are summed up in Figure 5.

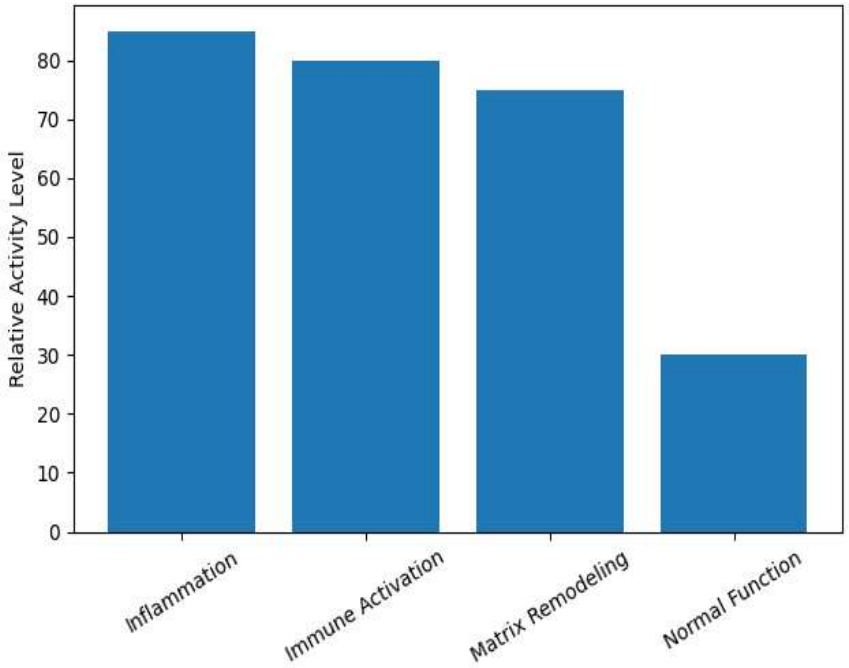

Figure 5: Integrated Mechanistic Insight into Plaque Progression

DISCUSSION

The current research has offered transcriptomic data to capacitance the main part in the pathogenesis of atherosclerosis, one of the primary outcomes of cardiovascular disease. The patterns of the analyzed cases of the differential gene expression in early and advanced plaques reveal the transition towards a highly active state of inflammatory and immune-responsive. This is in line with the known facts that inflammatory signaling is a major cause of cardiovascular pathology that affects endothelial dysfunction, vascular remodeling, and plaque instability (Zhang & Dhalla, 2024). The functional enrichment of gene expression alteration is another point that supports the idea that inflammation can be of the nature of both molecular and systemic mode of disease progress.

The observation of core regulating genes in the interaction network indicates that a certain hub of molecules regulates the inflammatory reactions and cell-cell communication in atherosclerotic plaques. The results are in line with genomic research that indicates that gene networks of inflammation are essential in vulnerability and progression of cardiovascular disease (Dhande & Doris, 2021). In addition, it is demonstrated that macrophage polarization and pro-inflammatory signaling are activated in the atherosclerosis acceleration, especially when there is a disruption in metabolism or enzyme defect during the development of the disease (ALDH2 deficiency) (Rui et al., 2024). Such processes bring to focus the usefulness of molecular perturbations to promote inflammatory cascades and plaque formation.

The analysis of the immune cell infiltration revealed that inflammatory immune cells showed greater presence in advanced development of plaques in favor of immune activation as a cause of the disease progression. The presence of macrophages, T cells, and neutrophils are also reported to lead to the instability of the plaques and vascular damage due to the secretion of cytokines and proteolytic enzymes by them. The same immune-mediated processes have been witnessed in septic cardiac injury when cellular excess of inflammatory reaction results into dysfunction of the heart muscle and tissue edema (Fan & Wu, 2024). These similarities posit this hypothesis to the tissue damage by inflammation as a common pathological phenomenon in cardiovascular disorders.

Inflammatory environment of cardiovascular disease also has a significant contribution of metabolic factors. The example of obesity is conducive to chronic low-grade inflammation and has been hugely linked to arrhythmogenic mechanisms (atrial fibrillation) (Shu et al., 2023). The co-relation between vascular dysfunction and immune stimulation is also aggravated by the interaction of metabolic pressure and immune response. Further, vascular remodeling related to hypertension has been related to the existence of molecular interaction that facilitates changes in the structure and functions of blood vessels (Bai et al., 2022). Such results point to the fact that metabolic and hemodynamic instigating factors combined with inflammation contribute to the process of cardiovascular pathology.

There is also some new data regarding the importance of the interactions between systems and neurovascularity in regulating inflammation and cardiovascular disease. The neuroendocrine (oxytoxic mediated) and social mechanisms have demonstrated to mediate the increase of atherosclerosis via the brain to liver regulation (Ko et al., 2024). This broadens the scope of cardiovascular disease into the local vascular processes broader into the globular regulatory networks. Equally, vascular inflammation was found to play a role in cerebrovascular damage and microhemorrhages of

neurodegenerative diseases, which suggests that there are similar inflammatory processes in organ systems (Taylor et al., 2024).

Based on this, the integrated mechanistic model obtained can be used to show how more complicated atherosclerotic plaques are typified with the formation of coordinated inflammatory pathways and elevated immune cell influx and tight exchange of signals among regulatory genes. These results can be supported by the notion that cardiovascular disease is a complication of multifaceted relationships between hereditary deviation, metabolic disorders, and immune disorders. The combination of these aspects results in a vicious cycle of inflammation and tissue damage which eventually results in the development of a disease.

Although this study had strengths, e.g., human transcriptomic data and multi-level analysis were used, there are some limitations that one may take into considerations. The results are compared using one dataset, which can be disadvantageous in the generalization of the results to other populations. Also, computational results of immune cell infiltration and network interactions have to be validated with the experiments to prove their biological validity. Further research that incorporates multi-omics with clinical validation will be required in the future to explain the mechanisms found.

Finally, the results offer an in-depth support to conclude that inflammation is an important point of centrality between a molecular modification and cardiovascular disease development. The discovery of major regulatory genes and pathways provides possible targets of intervention therapy. Advancing the multitasking mechanism between inflammation, immune activation, and metabolic regulation towards the formulation of the effective strategies of prevention and treatment of cardiovascular disease will be necessary.

CONCLUSION

The current research article gives a transcriptomic insight into the molecular pathways of inflammation to cardiovascular disease, especially within the atherosclerotic pathogenesis. The analysis of early and advanced lesions showed that the presence of early and advanced plaques was different in terms of gene expression which is amplified on inflammatory signaling, immune activation, and inhibition of normal vascular functions in advanced lesions. These data confirm the idea that atherosclerosis is an inflammation disease, in essence. The activation of important inflammatory pathways and central regulatory genes by functional enrichment and network analysis also emphasized that important interactions in the microenvironment of the plaque are organized by these molecules. The fact that the infiltration of immune cells in the advanced plaques has been observed increases with the critical role of the innate and adaptive immune responses in the development of the disease. A combination of molecular and cellular data indicates an orchestrated and positive-feedback mechanism of action of inflammatory cascade that contributes to the development and instability of the plaque. In general, the present research paper provides a mechanistic association between inflammation and cardiovascular disease at the transcriptomic level. The discovered genes and pathways are advantageous to the biomarkers and treatment targeting. It is justified that future research with experimental validation, multi-omics research is introduced to further narrow the gap of these results and translate them into clinical practice to enhance the management of cardiovascular diseases.

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