Integration of Molecular Factors Influencing VCAM-1 Expression in Vascular Inflammation and Atherosclerosis: A Narrative Review

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Abstract

Vascular Cell Adhesion Molecule-1 (VCAM-1) is a vascular adhesion molecule that plays a crucial role in vascular inflammation, endothelial dysfunction, and the development of atherosclerosis. Increased VCAM-1 expression occurs in response to various inflammatory stimuli and cellular stressors that involve the activation of specific molecular signaling pathways. Various factors such as chronic inflammation, oxidative stress, activation of the Nuclear Factor-kappa B (NF-κB) pathway, the Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway, obesity, leptin resistance, genetic factors, and changes in vascular hemodynamics are known to contribute to increased VCAM-1 expression. This study aims to analyze various factors that influence VCAM-1 changes molecularly using a narrative review method. Article searches were conducted through the PubMed, Scopus, and Google Scholar databases using the keywords "VCAM-1", "NF-κB", "oxidative stress", "LEPR", "leptin resistance", "endothelial dysfunction", and "atherosclerosis". The articles used were published between 2020 and 2026, relevant to the research topic, and available in full text. The review results indicate that NF-κB activation is the primary mechanism of VCAM-1 elevation triggered by pro-inflammatory cytokines, increased reactive oxygen species (ROS), leptin resistance, and LEPR activation via the JAK-STAT pathway. Furthermore, genetic factors such as LEPR polymorphisms and epigenetic mechanisms also contribute to increased vascular inflammation and VCAM-1 expression. Thus, VCAM-1 has great potential as a biomarker of vascular inflammation and a therapeutic target in cardiovascular disease, particularly atherosclerosis.

Keywords: *VCAM-1, NF-κB, JAK-STAT, Leptin Resistance, Atherosclerosis.*

A. INTRODUCTION

Cardiovascular diseases remain the leading contributors to global mortality and morbidity rates. The pathogenesis of these conditions is closely associated with chronic inflammation, obesity, oxidative stress, and vascular endothelial dysfunction. One of the crucial mechanisms involved in the early stages of atherosclerosis is the increased adhesion of leukocytes to the vascular endothelium mediated by adhesion molecules, particularly Vascular Cell Adhesion Molecule-1 (VCAM-1). As a transmembrane glycoprotein belonging to the immunoglobulin superfamily, VCAM-1 is synthesized by endothelial cells in response to inflammatory stimuli. The upregulation of VCAM-1 expression promotes the adhesion of monocytes and lymphocytes, which subsequently migrate into the intimal layer and contribute to the formation of atherosclerotic plaques. Therefore, VCAM-1 possesses substantial significance as both a predictive biomarker and a strategic therapeutic target for inhibiting the progression of cardiovascular diseases.

At the molecular level, alterations in VCAM-1 expression are regulated by highly complex and multifactorial mechanisms. Chronic inflammation induces the release of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, which subsequently activate the NF-κB signaling pathway. In addition, oxidative stress resulting from the accumulation of reactive oxygen species (ROS) further mediates vascular inflammatory activation. In the metabolic context, obesity and leptin resistance contribute to systemic inflammation through the activation of the Leptin Receptor (LEPR), involving both the JAK-STAT and NF-κB signaling pathways. Genetic factors, such as LEPR polymorphisms, epigenetic modifications, and biophysical factors including low wall shear stress, have also been reported to modulate endothelial sensitivity in expressing VCAM-1.

Although the functional roles of these variables have been extensively investigated individually, an integrated synthesis encompassing classical signaling pathways, mechanobiology, and epigenetic regulation within a single comprehensive review framework remains considerably limited. Such an integrated understanding is critically required to formulate more precise and targeted medical intervention strategies. Therefore, this narrative review aims to provide an in-depth analysis of the integration of various molecular factors influencing VCAM-1 dynamics by referring to the most recent scientific literature published between 2020 and 2026.

B. METHOD

This study employed a narrative review approach to evaluate various molecular factors involved in the alteration of VCAM-1 expression in vascular inflammation and atherosclerosis. The literature search was conducted through several scientific databases, including PubMed, Scopus, and Google Scholar. The search strategy utilized combinations of keywords and Boolean operators as follows: ("VCAM-1" OR "vascular cell adhesion molecule-1") AND ("NF-κB" OR "JAK-STAT" OR "leptin resistance" OR "atherosclerosis" OR "endothelial dysfunction").

Articles published between 2020 and 2026 were screened based on their relevance to the research topic. The inclusion criteria were as follows:

1. Articles discussing the molecular regulation of VCAM-1.
2. Studies addressing vascular inflammation or atherosclerosis.
3. Full-text articles available for review.
4. Articles published in indexed scientific journals.

The exclusion criteria included:

1. Duplicate articles.
2. Articles that did not specifically discuss VCAM-1.
3. Editorials, commentaries, or non-scientific articles.
4. Articles containing data irrelevant to the focus of the study.

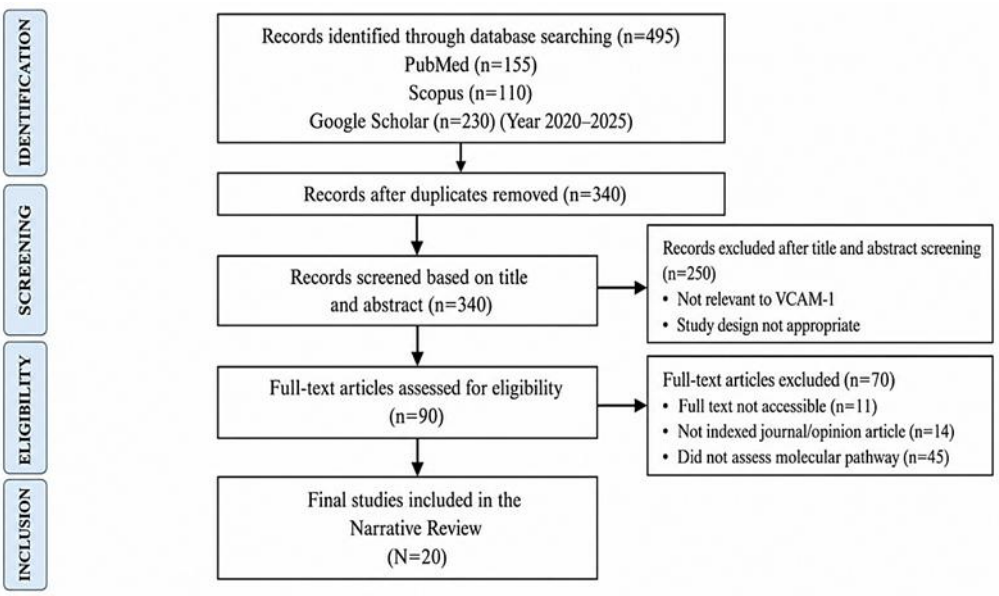

Figure 1. PRISMA Diagram of Various Molecular Factors Influencing VCAM-1 Alterations

C. RESULT AND DISCUSSION

To identify the molecular mechanisms underlying the regulation of Vascular Cell Adhesion Molecule-1 (VCAM-1) expression, a comprehensive review of relevant studies was conducted. Various molecular factors have been reported to influence VCAM-1 expression through distinct signaling pathways, transcription factors, inflammatory mediators, and oxidative stress mechanisms. Understanding these molecular interactions is essential because VCAM-1 plays a crucial role in endothelial dysfunction, leukocyte adhesion, and the progression of inflammatory and cardiovascular diseases. The literature analysis presented in Table 1 summarizes the key molecular factors, their mechanisms of action, and their reported effects on VCAM-1 expression across different experimental and clinical studies.

Table 1. Literature Analysis of Molecular Factors Influencing VCAM-1 Expression

No	Authors	Research Focus	Molecular Mechanism	Main Findings	Literature Analysis
1	Yu et al., 2020	NF-κB in inflammation	NF-κB activation enhances the transcription of inflammatory mediators	VCAM-1 expression increased	NF-κB acts as a major regulator of vascular inflammation
2	Sarapultsev et al., 2023	JAK-STAT pathway	JAK-STAT activation promotes chronic inflammation	Inflammatory response increased	JAK-STAT reinforces NF-κB activation
3	Groten et al., 2025	NF-κB and JAK-STAT	Simultaneous inhibition suppresses endothelial inflammation	VCAM-1 expression decreased	Both pathways function synergistically

4	Hernandez et al., 2021	Hyperleptinemia	Leptin enhances inflammatory mediators	Vascular inflammation increased	Leptin aggravates atherosclerosis
5	Raman & Khanal, 2021	Leptin in atherosclerosis	Leptin promotes monocyte adhesion	VCAM-1 expression increased	Leptin accelerates plaque formation
6	Liu et al., 2022	Leptin resistance	Impaired leptin signaling pathways	Systemic inflammation increased	Leptin resistance intensifies inflammation
7	Hu et al., 2025	Obesity and leptin	Hyperleptinemia increases ROS production	Oxidative stress increased	Obesity accelerates vascular inflammation
8	Higashi, 2022	Endothelial dysfunction	ROS reduces nitric oxide bioavailability	VCAM-1 expression increased	ROS triggers vascular damage
9	Shaito et al., 2022	ROS and inflammation	ROS activates NF-κB signaling	Vascular inflammation increased	NF-κB serves as a key inflammatory mediator
10	Yan et al., 2024	Disturbed flow	TLR2/TLR4 activation stimulates NF-κB signaling	VCAM-1 expression increased	Innate immunity influences VCAM-1 regulation
11	Cheng et al., 2023	Vascular mechanobiology	Disturbed blood flow enhances endothelial inflammation	Endothelial activation increased	Hemodynamic factors influence VCAM-1 expression
12	Wang et al., 2023	Disturbed flow and ROS	Hemodynamic forces affect endothelial regulation	VCAM-1 regulation altered	Mechanical factors contribute to inflammation
13	Chen et al., 2025	Epigenetic regulation of VCAM-1	Disturbed flow increases oxidative stress	Endothelial dysfunction increased	Hemodynamic factors exacerbate inflammation
14	Hu et al., 2021	LEPR polymorphism	HDAC1/2 regulates VCAM-1 expression	VCAM-1 expression altered	Epigenetic factors influence inflammation
15	Veerabathiran et al., 2023	LEPR and obesity	LEPR genetic variation affects metabolism	Metabolic risk increased	Genetic factors strengthen inflammation
16	Penes et al., 2024	LEPR rs1137101	LEPR variation associated with obesity phenotype	Obesity risk increased	Genetic factors aggravate leptin resistance
17	Supti et al., 2024	VCAM-1 as a biomarker	Polymorphism increases obesity risk	Metabolic dysfunction increased	Genetic variation enhances inflammation
18	Troncoso et al., 2021	VCAM-1 and ICAM-1	Endothelial activation increases VCAM-1 expression	Biomarker of atherosclerosis identified	VCAM-1 reflects vascular inflammation
19	Kaur et al., 2022	VCAM-1 as a therapeutic target	Adhesion molecules are upregulated	CVD progression increased	VCAM-1 correlates with inflammation

20	Pickett et al., 2023	Disturbed flow	Targeting VCAM-1 suppresses inflammation	Therapeutic potential increased	VCAM-1 is a promising therapeutic target

The articles included in this narrative review were derived from various international journals discussing vascular inflammation, atherosclerosis, endothelial dysfunction, VCAM-1, NF-κB, leptin, and oxidative stress. Most of the studies employed molecular experimental approaches, observational designs, and analyses of biological mechanisms.

1. **Integration of VCAM-1 in the Pathogenesis of Endothelial Dysfunction and Atherogenesis**

Vascular Cell Adhesion Molecule-1 (VCAM-1) plays a central role in the initiation of atherosclerosis through its ability to mediate leukocyte adhesion and migration to the endothelial surface (1,2). The expression of this molecule represents a major indicator of endothelial dysfunction, characterized by increased vascular permeability and reduced nitric oxide (NO) bioavailability (3). This molecular process culminates in the recruitment of leukocytes from the bloodstream to the vascular wall, an adhesive mechanism visually illustrated in Phase 4 of Figure 2 (1). Furthermore, VCAM-1 regulation is highly dynamic and influenced by epigenetic mechanisms, in which HDAC1 and HDAC2 participate in regulating the GATA6 promoter (4).

2. **Synergistic Interaction Between NF-κB and JAK-STAT Signaling Pathways**

Initial activation induced by hyperleptinemia (Phase 1) triggers intracellular signaling cascades (Phase 2), ultimately culminating in VCAM-1 expression within the nucleus (Phase 3) (5).

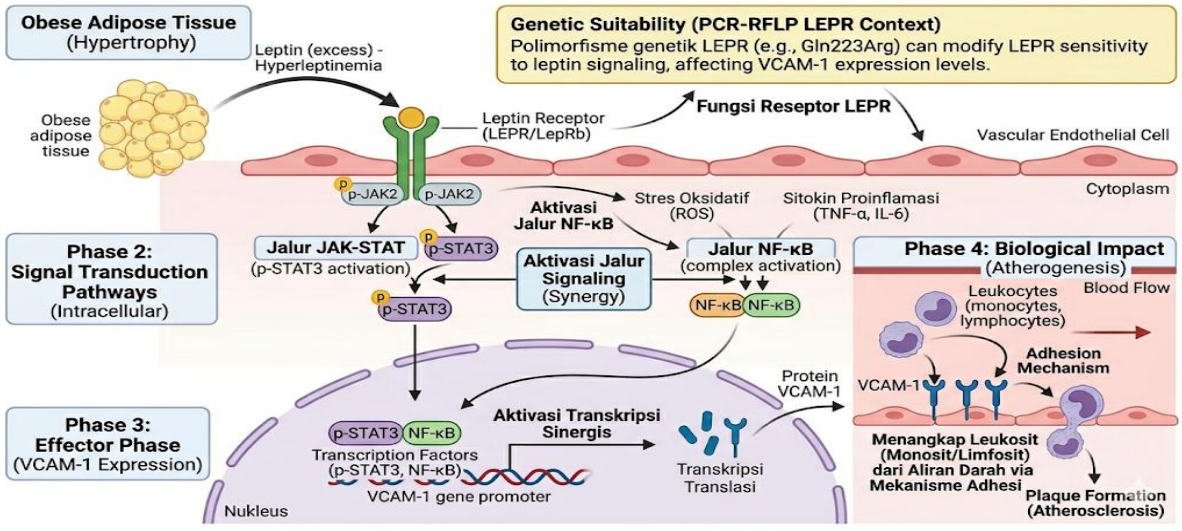

Figure 2. Molecular Mechanism of the Synergistic Activation of NF-κB and JAK-STAT Pathways in the Regulation of VCAM-1 Expression under Obesity Conditions (6).

VCAM-1 activation in endothelial cells is tightly regulated by a complex network of interacting intracellular signaling pathways, particularly the NF-κB and JAK-STAT pathways:

a. NF-κB as the Primary Regulator: This pathway functions as a principal molecular switch that responds to various pro-inflammatory stimuli, including TNF-α, IL-1β, IL-6, oxidative stress, and metabolic conditions such as hyperglycemia (7,8).
b. Complementary Role of JAK-STAT: The JAK-STAT pathway, particularly through STAT3 phosphorylation, amplifies metabolic inflammatory responses associated with leptin resistance (9,10).
c. Therapeutic Synergy: Literature analysis indicates that combined inhibition of the NF-κB and JAK-STAT pathways produces a more pronounced anti-inflammatory effect compared with single-pathway inhibition, thereby highlighting the crucial synergistic interaction involved in the regulation of vascular adhesion molecules (6).

The synergistic mechanisms between the NF-κB and JAK-STAT pathways that induce VCAM-1 transcription are comprehensively illustrated within the molecular framework presented in Figure 1 (Phases 2 and 3).

3. Pathological Axis of Obesity, Leptin Resistance, and Oxidative Stress

The molecular cascades described above are frequently initiated by systemic metabolic disturbances such as obesity (11). Obesity contributes to the progression of cardiovascular diseases through chronic inflammatory conditions and hyperleptinemia (12). Under leptin-resistant conditions, dysregulation of signaling pathways mediated by the Leptin Receptor (LEPR) triggers increased production of Reactive Oxygen Species (ROS) (10,13). The elevation of ROS subsequently activates the NF-κB pathway, thereby creating a vicious inflammatory cycle that accelerates VCAM-1 expression and facilitates monocyte adhesion during atherosclerotic plaque formation (8,14). This variability in inflammatory response is also influenced by genetic factors, particularly LEPR rs1137101 polymorphisms (15,16).

4. Contribution of Mechanobiological, Genetic, and Epigenetic Factors

Biophysical factors, particularly hemodynamic alterations, play a substantial role in vascular inflammation (17). Low wall shear stress or disturbed flow has been demonstrated to induce endothelial cell reprogramming, significantly increasing endothelial sensitivity to inflammatory cytokines and enhancing VCAM-1 expression (18,19). This variability in vascular response is also genetically determined; polymorphisms in the LEPR gene (such as rs1137101) influence individual leptin sensitivity and increase the risk of systemic inflammation (15). Furthermore, this regulatory process is refined by epigenetic mechanisms through the involvement of HDAC1 and HDAC2 in regulating the GATA6 promoter, indicating that VCAM-1 expression is controlled by a dynamic interaction among mechanical environments, metabolic status, and chromatin structure (4). Unlike static genetic polymorphisms, epigenetic regulation mediated by HDAC1/2 provides therapeutic opportunities through the application of HDAC inhibitors as novel pharmacological strategies for suppressing VCAM-1 expression (4).

5. Clinical Implications: VCAM-1 as a Precision Therapeutic Target

The close association between VCAM-1 levels and the progression of atherosclerotic plaques has established VCAM-1 as a reliable predictive biomarker in clinical management (2,20). Recent advances in therapeutic strategies have increasingly focused on interventions specifically targeting VCAM-1, including the utilization of extracellular vesicles (21). This approach offers the potential for more localized therapeutic delivery to inflamed vascular regions while minimizing systemic adverse effects. The importance of dual-targeted therapeutic strategies was further emphasized by recent experimental findings reported by (6), demonstrating that simultaneous inhibition of the NF-κB and JAK-STAT pathways resulted in more substantial suppression of endothelial inflammation and greater reduction of VCAM-1 expression compared with single-pathway inhibition. These findings provide strong evidence that the synergistic interaction between these two pathways serves as a critical mechanism underlying the amplification of vascular inflammatory signaling.

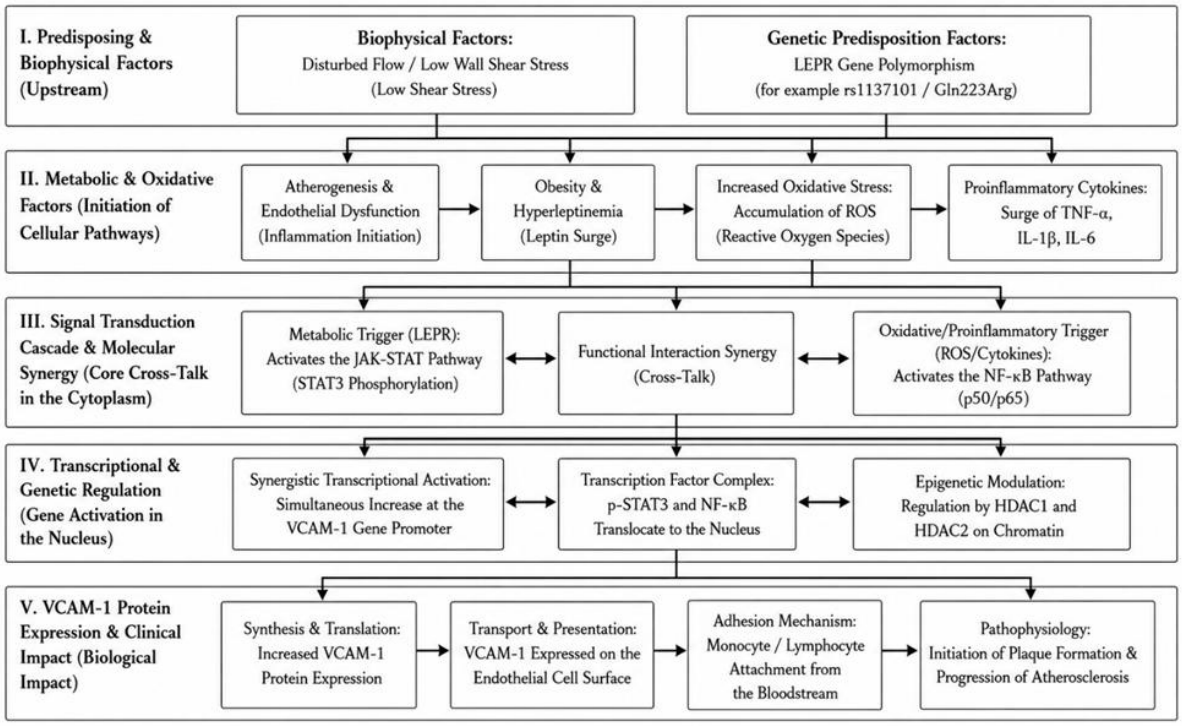

Figure 3. Diagram of Factors Influencing VCAM-1 Dynamics (7,12).

This pathway demonstrates that the upregulation of VCAM-1 is not the result of a single signaling pathway, but rather represents a multifactorial manifestation involving the interaction of biophysical, metabolic, and genetic factors..

6. Interaction Between Upstream and Midstream Stimuli

The initiation process begins with genetic predisposition factors, particularly LEPR gene polymorphisms (such as rs1137101), which influence receptor sensitivity to leptin (15). When accompanied by obesity, this condition triggers hyperleptinemia and leptin resistance, both of which serve as major drivers of systemic inflammation (10,12). Simultaneously, mechanobiological factors such as disturbed flow or low wall

shear stress provide biophysical signals that enhance endothelial cell susceptibility to oxidative stress and pro-inflammatory cytokines, including TNF-α and IL-6 (19).

7. Synergistic Interaction of Signaling Pathways (Novelty Point)

The core of this theoretical framework lies in the functional synergy (cross-talk) between intracellular biochemical signaling pathways. Metabolic stimuli mediated through LEPR activation induce the JAK-STAT cascade, particularly STAT3 phosphorylation, whereas oxidative and cytokine-mediated stimuli activate the NF-κB pathway (6). These two pathways operate synergistically, in which inhibition of a single pathway alone has been shown to be insufficient for fully suppressing VCAM-1 expression compared with simultaneous inhibitory approaches targeting both pathways (6,8).

8. Genetic Regulation and Biological Impact

At the nuclear level, p-STAT3 and NF-κB complexes simultaneously bind to the VCAM-1 gene promoter, a process further refined by epigenetic mechanisms involving HDAC1 and HDAC2 regulation (4). The result of this synergistic transcriptional activation is the escalation of VCAM-1 protein production expressed on the endothelial surface (7). Clinically, this phenomenon initiates the adhesion of monocytes and lymphocytes from the bloodstream, representing a fundamental stage in the initiation of atherosclerotic plaque formation (1,2).

D. CONCLUSION

Based on a comprehensive analysis of recent literature, it can be concluded that VCAM-1 is not merely a passive marker, but rather a crucial active mediator involved in the initiation and progression of atherosclerosis through the facilitation of leukocyte adhesion to the vascular endothelium. Its expression is regulated through a complex synergistic interaction between the NF-κB and JAK-STAT signaling pathways. Systemic metabolic factors such as obesity and leptin resistance have been demonstrated to exacerbate vascular inflammation by triggering a pathological axis involving LEPR activation and increased oxidative stress (ROS), which subsequently amplifies VCAM-1 transcriptional signaling.

Interindividual variability in VCAM-1 expression is significantly influenced by genetic determinants, including LEPR rs1137101 polymorphisms, as well as epigenetic regulation mediated through histone acetylation mechanisms. The integration of biochemical and mechanobiological factors, particularly low wall shear stress, further emphasizes the role of VCAM-1 as a converging point of multiple vascular pathophysiological pathways. Therefore, VCAM-1 possesses substantial potential as both a reliable predictive biomarker and a precision therapeutic target, including through the application of extracellular vesicle-based interventions, in efforts to reduce the future burden of cardiovascular diseases.

REFERENCES

1. Raman, P., & Khanal, S. (2021). Leptin in atherosclerosis: focus on macrophages, endothelial and smooth muscle cells. *International journal of molecular sciences*, *22*(11), 5446.
2. Troncoso, M. F., Ortiz-Quintero, J., Garrido-Moreno, V., Sanhueza-Olivares, F., Guerrero-Moncayo, A., Chiong, M., ... & Lavandero, S. (2021). VCAM-1 as a predictor biomarker in cardiovascular disease. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1867*(9), 166170.
3. Higashi, Y. (2022). Roles of oxidative stress and inflammation in vascular endothelial dysfunction-related disease. *Antioxidants*, *11*(10), 1958.
4. Hu, C., Peng, K., Wu, Q., Wang, Y., Fan, X., Zhang, D. M., ... & Sun, C. (2021). HDAC1 and 2 regulate endothelial VCAM-1 expression and atherogenesis by suppressing methylation of the GATA6 promoter. *Theranostics*, *11*(11), 5605.
5. Hernandez, V., Kaur, K., ElSharief, M. W., Al Hajaj, S. W., Ebrahim, A. M., Razack, M., ... & Hernandez, V. K. (2021). The new kid on the block: the mechanisms of action of hyperleptinemia in coronary artery disease and atherosclerosis. *Cureus*, *13*(6).
6. Groten, S. A., Langerhorst, P., Malamas, G., Barraclough, A., Hoogendijk, A. J., & van den Biggelaar, M. (2025). Targeting synergetic endothelial inflammation by inhibiting NFKB and JAK-STAT pathways. *iScience*, *28*(9).
7. Yu, H., Lin, L., Zhang, Z., Zhang, H., & Hu, H. (2020). Targeting NF-κB pathway for the therapy of diseases: mechanism and clinical study. *Signal transduction and targeted therapy*, *5*(1), 209.
8. Shaito, A. A., Aramouni, K., Assaf, R. K., Parenti, A., Orekhov, A. N., Yazbi, A. E., ... & Eid, A. H. (2022). Oxidative stress-induced endothelial dysfunction in cardiovascular diseases.
9. Sarapultsev, A., Gusev, E., Komelkova, M., Utepova, I., Luo, S., & Hu, D. (2023). JAK-STAT signaling in inflammation and stress-related diseases: implications for therapeutic interventions. *Molecular biomedicine*, *4*(1), 40.
10. Liu, J., Lai, F., Hou, Y., & Zheng, R. (2022). Leptin signaling and leptin resistance. *Medical review*, *2*(4), 363-384.
11. Penes, O. N., Weber, B., Pop, A. L., Bodnarescu-Cobanoglu, M., Varlas, V. N., Kucukberksun, A. S., ... & Zetu, C. (2024). Gene Polymorphisms LEP, LEPR, 5HT2A, GHRL, NPY, and FTO-Obesity Biomarkers in Metabolic Risk Assessment: A Retrospective Pilot Study in Overweight and Obese Population in Romania. *Cardiogenetics*, *14*(2), 93-105.
12. Hu, W., Zhu, H., & Gong, F. (2025). Leptin and leptin resistance in obesity: current evidence, mechanisms and future directions. *Endocrine Connections*, *14*(9).
13. Yan, B., Yu, X., Cai, X., Huang, X., Xie, B., Lian, D., ... & Li, J. (2024). A review: the significance of toll-like receptors 2 and 4, and NF-κB signaling in endothelial cells during atherosclerosis. *Frontiers in Bioscience-Landmark*, *29*(4), 161.

14. Yan, Q., Liu, S., Sun, Y., Chen, C., Yang, S., Lin, M., ... & Yang, Y. (2023). Targeting oxidative stress as a preventive and therapeutic approach for cardiovascular disease. *Journal of translational medicine*, *21*(1), 519.
15. Supti, D. A., Akter, F., Rahman, M. I., Munim, M. A., Tonmoy, M. I. Q., Tarin, R. J., ... & Hossain, M. S. (2024). Meta-analysis investigating the impact of the LEPR rs1137101 (A> G) polymorphism on obesity risk in Asian and Caucasian ethnicities. *Heliyon*, *10*(6).
16. Veerabathiran, R., P, A., Bk, I., & RS, A. H. (2023). Genetic predisposition of LEPR (rs1137101) gene polymorphism related to type 2 diabetes mellitus–a meta-analysis. *Annals of medicine*, *55*(2), 2302520.
17. Wang, X., Shen, Y., Shang, M., Liu, X., & Munn, L. L. (2023). Endothelial mechanobiology in atherosclerosis. *Cardiovascular research*, *119*(8), 1656-1675.
18. Cheng, H., Zhong, W., Wang, L., Zhang, Q., Ma, X., Wang, Y., ... & Fu, C. (2023). Effects of shear stress on vascular endothelial functions in atherosclerosis and potential therapeutic approaches. *Biomedicine & Pharmacotherapy*, *158*, 114198.
19. Chen, J. W., Chen, S. L., Wu, X. R., Shu, X. Y., Tang, S. Y., Yuan, H., ... & Wang, X. Q. (2025). 12/15-lipoxygenase mediates disturbed flow-induced endothelial dysfunction and atherosclerosis. *Molecular Medicine*, *31*(1), 257.
20. Kaur, R., Singh, V., Kumari, P., Singh, R., Chopra, H., & Emran, T. B. (2022). Novel insights on the role of VCAM-1 and ICAM-1: Potential biomarkers for cardiovascular diseases. *Annals of medicine and surgery*, *84*.
21. Pickett, J. R., Wu, Y., Zacchi, L. F., & Ta, H. T. (2023). Targeting endothelial vascular cell adhesion molecule-1 in atherosclerosis: drug discovery and development of vascular cell adhesion molecule-1–directed novel therapeutics. *Cardiovascular Research*, *119*(13), 2278-2293.