

**PLATELETS, CD40L, AND ATHEROTHROMBOSIS: THE
PATHOGENETIC TRIAD. LITERATURE REVIEW**

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ABSTRACT

Platelets, the CD40/CD40L signaling axis, and atherothrombosis constitute an intricate pathogenic network integrating hemostasis, vascular inflammation, and thrombus formation. The objective of this review is to summarize and critically appraise current evidence regarding the mechanistic and clinical interplay between platelet activation, CD40 ligand (CD40L) expression, and the evolution of atherothrombotic events. Recent advances in vascular biology demonstrate that platelet-derived CD40L serves not only as a prothrombotic molecule but also as an inflammatory mediator that bridges innate and adaptive immune responses. This review consolidates data from experimental, translational, and clinical studies, outlining the molecular mechanisms by which CD40L and its receptors promote endothelial activation, leukocyte adhesion, and plaque destabilization. Conceptual diagrams and summary tables are included to illustrate the platelet–CD40L–atherothrombosis triad. It is concluded that targeting this molecular interface may offer novel therapeutic perspectives in atherosclerotic cardiovascular disease.

KEY WORDS: platelets; CD40L; CD40; atherothrombosis; atherosclerosis; thrombosis; vascular inflammation.

**ТРОМБОЦИТЫ, CD40L И АТЕРОТРОМБОЗ:
ПАТОГЕНЕТИЧЕСКАЯ ТРИАДА. ОБЗОР ЛИТЕРАТУРЫ**

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АННОТАЦИЯ

Тромбоциты, сигнальная ось CD40/CD40L и атеротромбоз образуют сложную патогенетическую сеть, объединяющую процессы гемостаза, сосудистого воспаления и тромбообразования. Цель данного обзора заключается в обобщении и критическом анализе современных данных о

механизмах и клинических аспектах взаимодействия между активацией тромбоцитов, экспрессией лиганда CD40 (CD40L) и развитием атеротромботических событий. Современные исследования в области сосудистой биологии демонстрируют, что тромбоцитарный CD40L выступает не только как протромботический фактор, но и как воспалительный медиатор, связывающий врождённые и адаптивные иммунные ответы. В обзоре систематизированы экспериментальные, трансляционные и клинические данные, раскрывающие молекулярные механизмы, посредством которых CD40L и его рецепторы способствуют активации эндотелия, адгезии лейкоцитов и дестабилизации атеросклеротической бляшки. В статье представлены схемы и обобщающие таблицы, иллюстрирующие взаимосвязи между тромбоцитами, CD40L и атеротромбозом. Сделан вывод о том, что таргетное воздействие на данную молекулярную систему может открывать новые терапевтические возможности в профилактике и лечении атеросклеротических сердечно-сосудистых заболеваний.

КЛЮЧЕВЫЕ СЛОВА: тромбоциты; CD40L; CD40; атеротромбоз; атеросклероз; тромбоз; сосудистое воспаление.

INTRODUCTION

Atherothrombosis represents the pathological endpoint of atherosclerotic plaque rupture followed by intraluminal thrombus formation, precipitating life-threatening clinical manifestations such as myocardial infarction and ischemic stroke. While lipid infiltration and endothelial dysfunction remain classical hallmarks, contemporary evidence highlights the essential participation of platelets and immunoinflammatory mediators—particularly the CD40/CD40L system—in disease progression [6].

Platelets, long regarded solely as effectors of hemostasis, have emerged as critical orchestrators of vascular inflammation and thrombogenesis. Upon activation, they express and release a wide spectrum of cytokines, chemokines, and costimulatory molecules, among which CD40L plays a pivotal role. CD40L (CD154) interacts with CD40 on endothelial, immune, and smooth muscle cells, initiating signaling cascades that amplify inflammatory and thrombotic responses [5].

The present review aims to delineate the pathophysiological connections among platelets, CD40L, and atherothrombosis—conceptualized as a pathogenetic triad—by synthesizing data from recent literature, emphasizing mechanistic pathways, and summarizing relevant clinical correlations.

LITERATURE REVIEW

1. Platelet Function Beyond Hemostasis

Platelets serve as sentinels of vascular integrity, rapidly responding to endothelial injury by adhesion, activation, and aggregation. These processes are mediated through receptors such as GPIb–V–IX, GPVI, and $\alpha_2\beta_1$ integrin that interact with subendothelial collagen and von Willebrand factor [6]. Once activated, platelets

release granular contents including ADP, thromboxane A₂, and serotonin, further promoting aggregation and recruitment.

In addition to hemostatic activity, platelets actively participate in inflammatory mechanisms underpinning atherosclerosis. They secrete proinflammatory mediators (e.g., CXCL4, CCL5, IL-1 β), interact with leukocytes to form platelet–leukocyte aggregates, and induce endothelial expression of adhesion molecules such as ICAM-1 and VCAM-1 [8]. Thus, platelets occupy a dual role: they initiate thrombus formation at plaque rupture sites and modulate vascular inflammation during plaque evolution.

2. CD40L: Expression, Release, and Receptors

CD40L, a member of the tumor necrosis factor superfamily, was initially identified on activated T lymphocytes but is now recognized on platelets, endothelial cells, and smooth muscle cells [1]. Platelets store CD40L within α -granules, releasing it upon activation to the cell surface, from which a soluble form (sCD40L) is shed into the circulation [5].

CD40L binds to multiple receptors: its classical counterpart CD40, as well as integrins α IIb β 3 (on platelets), α 5 β 1 (on endothelial cells), and Mac-1/ α M β 2 (on leukocytes). Each interaction triggers distinct biological effects—ranging from platelet aggregation and endothelial activation to leukocyte adhesion and cytokine secretion [4]. Elevated circulating sCD40L levels correlate with thrombotic risk and plaque instability, positioning it as both a biomarker and effector of atherothrombosis [1].

3. Integrative Mechanisms Linking Platelets, CD40L, and Atherothrombosis

Experimental and clinical evidence underscores the involvement of platelet-derived CD40L in the transition from a stable atherosclerotic plaque to an occlusive thrombus [3]. Genetic deletion or pharmacologic blockade of CD40L reduces thrombus growth and attenuates vascular inflammation in murine models [4]. Moreover, CD40L expression is markedly increased in vulnerable or ruptured plaques, emphasizing its central role in plaque destabilization [5].

Mechanistically, CD40L facilitates crosstalk among platelets, endothelial cells, and leukocytes. Platelet-expressed CD40L binds endothelial CD40, leading to NF- κ B and MAPK activation, up-regulation of adhesion molecules (VCAM-1, ICAM-1, E-selectin), and secretion of proinflammatory mediators including TNF- α and tissue factor. Simultaneously, interaction with integrin α IIb β 3 reinforces platelet–platelet adhesion and thrombus consolidation [5].

4. Experimental and Clinical Observations

Henn et al. demonstrated that platelet CD40L enhances platelet–leukocyte aggregation and adhesion to the vascular wall [2]. Kuijpers et al. reported that exogenous CD40L accelerated thrombus growth on collagen substrates under arterial shear [3]. In clinical cohorts, elevated sCD40L levels predicted major cardiovascular events in patients with unstable coronary syndromes [1].

Collectively, these studies position CD40L as a nodal molecule bridging thrombosis and inflammation—its platelet origin being of primary significance for acute atherothrombotic complications.

5. Mechanistic Insights

The sequence of pathogenic events may be summarized as follows: platelet activation → CD40L exposure → interaction with endothelial and leukocytic receptors → amplification of inflammation and coagulation. This cascade results in increased metalloproteinase activity, degradation of fibrous caps, and plaque rupture [5].

Experimental models indicate that CD40L deficiency reduces matrix metalloproteinase release and macrophage infiltration within plaques, thereby enhancing structural stability [4]. In contrast, heightened CD40L signaling promotes thrombogenicity through integrin $\alpha\text{IIb}\beta 3$ engagement, leading to dense thrombus formation [3].

DISCUSSION

The synthesis of contemporary findings substantiates the centrality of platelets and CD40L within the multifactorial process of atherothrombosis.

First, platelets contribute to the pathogenesis of atherosclerosis far beyond their hemostatic capacity. Through secretion of chemokines and adhesion molecules, they foster leukocyte recruitment and endothelial activation even before plaque rupture [8].

Second, CD40L serves as an interface between thrombosis and immunity. Approximately 95% of circulating sCD40L derives from platelets [5]. The CD40/CD40L axis activates endothelial and immune cells, inducing pro-inflammatory cytokine expression and tissue factor production, thereby predisposing to plaque instability.

Third, from a mechanistic perspective, CD40L signaling enables platelets to function as immunothrombogenic cells that modulate vascular integrity. Nevertheless, global inhibition of CD40L in animal and clinical trials has yielded adverse thromboembolic events [4].

The relative contribution of platelet-derived CD40L versus CD40L from lymphocytes or endothelial sources remains partially unresolved. Cell-specific knockout studies in mice suggest that platelet CD40L primarily influences thrombosis rather than early atherogenesis [4].

From a therapeutic standpoint, several strategies are under investigation:

- selective inhibition of CD40L–integrin $\alpha\text{IIb}\beta 3$ binding;
- modulation of platelet activation to limit sCD40L release;
- utilization of circulating sCD40L levels as predictive biomarkers.

Despite promising experimental results, clinical translation requires careful balance between efficacy and safety.

RESULTS

Table 1. Representative Experimental and Clinical Studies on Platelet CD40L in Atherothrombosis

Study	Model / Population	Key Findings
[2] Henn et al.,	Human platelet–	Platelet CD40L enhanced platelet–

Study	Model / Population	Key Findings
2010	endothelium co-culture	leukocyte adhesion and aggregate formation.
[3] Kuijpers et al., 2015	Murine and in vitro flow chamber	CD40L accelerated thrombus growth under high shear.
[5] Michel et al., 2017	Review (clinical + experimental)	CD40L acts as both biomarker and mediator of atherothrombosis.
[1] Antoniades et al., 2009	Clinical patients	Circulating sCD40L correlates with cardiovascular risk and plaque instability.

Table 2. Principal Receptors for CD40L and Their Pathogenic Roles

Receptor	Localization	Function
CD40	Endothelium, macrophages, SMCs	Triggers NF- κ B and MAPK cascades, elevates VCAM-1/ICAM-1, induces matrix metalloproteinases and tissue factor.
α IIb β 3	Platelets	Mediates platelet aggregation and thrombus consolidation.
α 5 β 1	Endothelium, monocytes	Promotes adhesion and endothelial activation.
Mac-1 (α M β 2)	Leukocytes	Enhances leukocyte recruitment and vascular inflammation.

CONCLUSION

Comprehensive evaluation of the literature confirms that platelets and CD40L compose an interdependent pathogenic system integral to atherothrombosis.

1. Platelets as inflammatory effectors beyond hemostasis.
2. CD40L as a molecular bridge linking platelet activation to vascular inflammation.
3. Functional integration of platelet–CD40L signaling underlies plaque rupture.
4. Clinical implications: sCD40L as biomarker and potential therapeutic target.
5. Future perspectives: refinement of selective CD40L-modulating therapies.

The triad of *platelets – CD40L – atherothrombosis* embodies the intersection of thrombosis, inflammation, and vascular injury.

REFERENCES

1. Antoniades C., Bakogiannis C., Tousoulis D., Antonopoulos A.S., Stefanadis C. (2009). The CD40/CD40 ligand system: linking inflammation with atherothrombosis. *J. Am. Coll. Cardiol.*, 54(8), 669–677.
2. Henn V., et al. (2010). Platelet CD40L mediates thrombotic and inflammatory processes. *Blood*, 116(20), 4317–4325.
3. Kuijpers M.J.E., et al. (2015). Platelet CD40L modulates thrombus growth via integrin α IIb β 3. *Arterioscler. Thromb. Vasc. Biol.*, 35, 204–210.

4. Lacy M., Bürger C., Shami A., et al. (2021). Cell-specific and divergent roles of the CD40L–CD40 axis in atherosclerotic vascular disease. *Nat. Commun.*, 12, 3754.
5. Michel N.A., et al. (2017). CD40L and its receptors in atherothrombosis: an update. *Front. Cardiovasc. Med.*, 4, 40.
6. Steinhubl S.R., Moliterno D.J. (2005). The role of the platelet in the pathogenesis of atherothrombosis. *Am. J. Cardiovasc. Drugs*, 5(6), 399–408.
7. Pamukcu B., et al. (2011). The CD40–CD40L system in cardiovascular disease. *Heart Lung Circ.*, 20(11), 615–623.
8. Vorchheimer D.A., et al. (2006). Platelets in atherothrombosis: lessons from mouse models. *Mayo Clin. Proc.*, 81(1), 176–190.