International Journal of Academic Health and Medical Research (IJAHMR)
ISSN: 2643-9824
Vol. 9 Issue 10 October - 2025, Pages: 46-51

The Contribution of Platelet CD40L (CD154) to the Activation of Proinflammatory and Procoagulant Pathways in Atherogenesis

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ABSTRACT: Platelet activation, a key component of hemostasis, also plays a crucial role in the pathogenesis of atherosclerosis through modulation of inflammatory and procoagulant processes. One of the central molecular mediators of these effects is CD40L (CD154), expressed on platelets and released in a soluble form. This review summarizes current literature regarding the role of platelet-derived CD40L in the initiation and maintenance of inflammation, endothelial activation, platelet–leukocyte aggregate formation, as well as in the activation of procoagulant pathways and stabilization of thrombotic structures. Special attention is given to signaling mechanisms (TRAF, MAPK, and others), interactions with CD40 on various vascular wall cells and integrin receptors, and the prospects for targeted therapeutic interventions. Summary tables of key findings and schematic representations of molecular interactions are provided. The review also discusses limitations of current approaches and outlines directions for future research.
KEY WORDS platelets, CD40L (CD154), atherogenesis, inflammation, thrombosis, coagulation, platelet–leukocyte interaction, endothelial activation.

INTRODUCTION

Atherosclerosis is currently recognized not merely as a passive accumulation of lipids within the arterial wall, but as a chronic inflammatory process in which immune and platelet components are tightly interconnected. The mechanisms linking thrombosis and inflammation — the so-called *thromboinflammation* — have gained increasing attention as important therapeutic targets. In this context, platelet CD40L (CD40 ligand, CD154) serves as a pivotal molecular mediator bridging platelet activation with the initiation of proinflammatory cascades and the activation of procoagulant pathways.

CD40L was initially characterized as a costimulatory molecule expressed on T-helper cells, interacting with CD40 on antigen-presenting cells. However, it has long been established that CD40L is also expressed on platelets, stored within α-granules, rapidly mobilized to the surface upon activation, and subsequently shed into plasma as a soluble form (sCD40L) [Antoniades et al., 2009, pp. 101–103; Michel et al., 2017, p. 3]. Approximately 95% of circulating sCD40L is derived from platelets, although other cellular sources are also possible [Michel et al., 2017, p. 4].

Experimental and model studies demonstrate that platelet-derived CD40L promotes thrombus formation, enhances platelet interactions with leukocytes and vascular wall cells, stimulates cytokine and chemokine release, and modulates coagulation pathways. Nevertheless, the specific contribution of platelet CD40L within the context of atherogenesis — as a factor amplifying inflammation and coagulation both within the atherosclerotic plaque and upon its disruption — requires more detailed and systematic examination.

The objective of this review is to analyze and integrate the existing evidence concerning the role of platelet CD40L in the activation of proinflammatory and procoagulant pathways during atherogenesis, to identify current knowledge gaps, and to discuss potential directions for future research and therapeutic strategies.

The structure of the review includes a comprehensive analysis of key literature, schematic representations of underlying mechanisms, summary tables, critical discussion points, and concluding remarks.

LITERATURE REVIEW

General Characteristics of Platelet CD40L: Expression, Mobilization, and Forms

Platelets store CD40L primarily within their α-granules and, upon activation (for example, by thrombin, collagen, or ADP), rapidly translocate it to the cell surface, where it assumes a trimeric, biologically active form. Subsequently, a portion of these surface-expressed molecules can be cleaved and released into the plasma as a soluble form (sCD40L) [Michel et al., 2017, p. 4; Antoniades et al., 2009, p. 102].

The shedding mechanisms involve metalloproteinases such as ADAM10, ADAM17, MMP-2, and MMP-9, and are likely influenced by the activation state of the integrin αIIbβ3 [Michel et al., 2017, pp. 4, 6]. It is estimated that approximately 95% of plasma sCD40L originates from platelets, underscoring their dominant role as the primary source of this molecule within the context of vascular pathophysiology [Michel et al., 2017, p. 4].

Functionally, platelet CD40L interacts with CD40 expressed on endothelial cells, vascular smooth muscle cells, monocytes/macrophages, and dendritic cells. In addition, it can bind to certain integrin receptors, such as α5β1, and under specific conditions, directly interact with platelet integrin αIIbβ3 [Michel et al., 2017, pp. 6, 8].

The Role of the CD40–CD40L System in Inflammation and Atherogenesis: General Context

The CD40–CD40L system has long been recognized as one of the central immuno-inflammatory pathways linking immune cell activation, endothelial activation, and vascular wall remodeling [Antoniades et al., 2009, p. 101; Langer et al., 2022, p. 1]. In the context of atherosclerosis, CD40L enhances the expression of adhesion molecules (VCAM-1, ICAM-1, and E-selectin) on endothelial cells, stimulates the release of proinflammatory cytokines (IL-1, IL-6, TNF-α) and chemokines (such as MCP-1/CCL2), and activates macrophages and dendritic cells via CD40 engagement. Through these interactions, CD40L/CD40 signaling amplifies inflammatory responses and promotes plaque progression [Antoniades et al., 2009, pp. 101–102; Michel et al., 2017, p. 2; Langer et al., 2022, p. 2].

Importantly, global inhibition of CD40L in experimental models has been associated with a marked reduction in atherosclerosis; however, such blockade may also lead to thrombus instability and thromboembolic complications. This highlights the need for selective and targeted approaches that can modulate the CD40–CD40L axis without compromising hemostatic balance [Lacy et al., 2021, p. 3; Michel et al., 2017, p. 10; Cognasse et al., 2022, p. 3].

Specifically: Platelet CD40L and Its Effects

Platelet–Leukocyte Interactions: Aggregate Formation and Leukocyte Activation

One of the most well-documented effects of platelet-derived CD40L is its role in the formation of platelet–leukocyte aggregates (e.g., platelet–monocyte and platelet–neutrophil complexes), which enhance leukocyte activation and promote their adhesion to the endothelium. In mouse experiments, the infusion of activated wild-type platelets significantly increased the formation of such aggregates, whereas CD40L-deficient platelets failed to elicit this effect [Lievens et al., 2010, pp. 4319–4323].

The presence of CD40 on leukocytes (monocytes and neutrophils) enables them to respond to platelet CD40L via activation of NF-κB and other intracellular signaling cascades, leading to enhanced synthesis of proinflammatory mediators. Deletion or blockade of CD40L markedly reduced leukocyte activation marker expression and decreased their adhesion to endothelial cells [Lievens et al., 2010, pp. 4322–4324].

Effects on the Endothelium and the Vascular Wall

Platelet-derived CD40L can interact with CD40 expressed on endothelial cells and trigger their activation, resulting in upregulation of adhesion molecules (VCAM-1, ICAM-1), secretion of chemokines and cytokines, and generation of reactive oxygen species (ROS). In cultured human endothelial cells, the addition of soluble CD40L (sCD40L) was shown to increase VCAM-1 and MCP-1 expression, an effect that was inhibited by anti-CD40 antibodies [Antoniades et al., 2009, p. 102]. Such actions facilitate monocyte recruitment to the vascular wall and their subsequent transmigration into the intima.

Furthermore, under conditions of plaque disruption, platelet CD40L may amplify local inflammatory responses by enhancing the expression of CCL2 (MCP-1). This has been demonstrated in immunohistological studies of atherosclerotic lesions in mice, where injections of activated wild-type platelets induced stronger local CCL2 expression compared with CD40L-deficient platelets [Lievens et al., 2010, pp. 4323–4325].

Procoagulant Effects and Thrombus Formation

CD40L enhances platelet aggregation and thrombus stability. In microcirculatory models under high shear stress, CD40L promotes platelet accumulation on collagen and stabilizes platelet aggregates [Lievens et al., 2010, pp. 4318–4320]. Mice deficient in CD40L exhibit delayed arterial occlusion and form less stable thrombi, an effect that can be partially restored by the administration of soluble CD40L (sCD40L) [Michel et al., 2017, p. 6; Antoniades et al., 2009, p. 103].

In addition, CD40L stimulates tissue factor (TF) expression in endothelial cells and monocytes, thereby enhancing the initiation phase of coagulation. The interaction of CD40L with CD40 on monocytes activates the NF-κB signaling pathway and promotes transcription of the tissue factor gene. This activation increases the local thromboinflammatory potential, particularly at sites of endothelial dysfunction [Antoniades et al., 2009, p. 102; Langer et al., 2022, p. 3].

Moreover, CD40L may potentiate the release of other procoagulant mediators from platelets—such as thromboxane A_2, factor V, and factor VIII—which collectively amplify the thrombogenic tendency within affected vascular regions.

Intracellular Signaling Mechanisms in Platelets

Following ligation of CD40L—whether through autocrine or paracrine interaction—platelets undergo activation of several intracellular signaling cascades, including TRAF-mediated pathways, Rac1 GTPase, and MAPK (p38) signaling, as well as potential activation of the α5β1 integrin and involvement of TRAF-2 (but not necessarily TRAF-6) [Michel et al., 2017, pp. 6–8]. These signaling events collectively promote platelet activation, surface expression of P-selectin, granule secretion, and stabilization of platelet aggregates [Michel et al., 2017, p. 8].

Interestingly, inhibition of α5β1 integrin reduces CD40L-induced platelet activation, as reflected by decreased P-selectin and PAC-1 expression. This finding suggests that α5β1 integrin may function as an auxiliary receptor for CD40L on platelets or, at least, participate in signal cross-talk with the CD40/CD40L complex [Michel et al., 2017, p. 8].

Influence on Regulatory T Cells and Immune-Mediated Effects

In murine studies, infusion of activated wild-type platelets produced a transient reduction in the frequency of regulatory T lymphocytes (Tregs) in peripheral blood and spleen — an effect not observed following infusion of CD40L-deficient platelets. Ablation of Tregs abolished the atheroprotective phenotype associated with CD40L deficiency, indicating that platelet-derived CD40L can modulate immune homeostasis via effects on Tregs and thereby amplify the prevailing inflammatory milieu. [Lievens et al., 2010, pp. 4324–4326].

Contextual Limitations: Impact on Plaque Progression versus Atherothrombotic Complications

Recent studies indicate that platelet-specific deletion of CD40L (e.g., using a Pf4-Cre model) does not always alter the size of atherosclerotic lesions, yet it markedly reduces susceptibility to thrombotic complications (for example, neointima formation) in models of atherothrombosis. These findings suggest that the role of platelet CD40L may be particularly relevant during complication-prone phases — thrombus formation and plaque destabilization — rather than in the canonical, progressive enlargement of the atheromatous plaque. [Lacy et al., 2021, pp. 5–6].

Overall, the evidence indicates that platelet CD40L not only augments platelet functions per se but also integrates these functions with immune–inflammatory mechanisms, acting as a key mediator of cross-talk between thrombosis and inflammation (thrombo-inflammation).

RESULTS

Summary of Data and Schemes

The following tables and schematic representations summarize key experimental findings from the literature, illustrating the major effects of **platelet-derived CD40L** and its intercellular interactions in thromboinflammation and vascular pathology.

Table 1. Principal Effects of Platelet-Derived CD40L and Corresponding Experimental Models

Effect / Phenomenon	Model / Experiment	Key Observations	Reference
Formation of platelet–leukocyte aggregates	Infusion of activated platelets into ApoE$^{-/-}$ mice	Increased platelet–leukocyte aggregates; significantly reduced in CD40L-deficient mice	[Lievens et al., 2010, pp. 4319–4323]
Leukocyte adhesion to endothelium	Intravital microscopy in murine arteries	Platelets expressing CD40L enhance leukocyte tethering; deficiency attenuates adhesion	[Lievens et al., 2010, pp. 4322–4325]
Plasma CCL2 (MCP-1) levels and endothelial expression	Serial platelet injections	Lower plasma and endothelial CCL2 levels in CD40L-deficient mice	[Lievens et al., 2010, pp. 4323–4325]
Rate of arterial occlusion / thrombus stability	Arterial thrombosis occlusion models	CD40L$^{-/-}$ mice exhibit delayed occlusion and unstable thrombi; restored by soluble CD40L (sCD40L)	[Michel et al., 2017, p. 6; Antoniades et al., 2009, p. 103]
Effect on regulatory T cells (Tregs)	Infusion of activated platelets	Transient reduction in Tregs observed only in CD40L-competent mice; absent in CD40L-deficient ones	[Lievens et al., 2010, pp. 4324–4326]
Effect on plaque size	Pf4-Cre CD40L-deficient mice on ApoE$^{-/-}$ background	Minimal changes in total plaque area but reduced thromboembolic complications	[Lacy et al., 2021, pp. 5–6]

Note: The references are presented in an abbreviated format for clarity in this table. Full citation details are provided in the *References* section.

Scheme 1. Mechanisms of Platelet CD40L Action in Atherosclerosis

[Platelet activation] → mobilization of membrane-bound CD40L → multiple cellular interactions:

1. **CD40L ↔ CD40 (on endothelial cells)** → ↑ VCAM-1 / ICAM expression, ↑ CCL2 production, ↑ ROS generation → *monocyte recruitment and endothelial activation*
2. **CD40L ↔ CD40 (on monocytes/macrophages)** → activation of **NF-κB** signaling → ↑ **tissue factor (TF)** and **pro-inflammatory cytokines**
3. **CD40L ↔ CD40 / α5β1 (on platelets)** → activation of **TRAF-2, p38 MAPK, Rac1** pathways → *platelet activation and granule secretion*
4. **CD40L–CD40 interaction promotes formation of platelet–leukocyte aggregates**, amplifying leukocyte activation and vascular inflammation
5. **Influence on Tregs:** reduction of regulatory T cells → shift toward a pro-inflammatory immune profile
6. **Contribution to thrombosis:** enhanced thrombus stability and activation of procoagulant pathways via **TF-dependent mechanisms**

Overall outcome: escalation of *thromboinflammation* and increased susceptibility to **thromboatherosclerotic complications**.

Scheme 2. Contextual Modulators and Limitations of Platelet CD40L Effects

Key factors influencing CD40L-mediated outcomes:

- **Lipid profile (hypercholesterolemia):** modifies baseline inflammatory tone and platelet activation thresholds.

- **Degree of endothelial dysfunction:** determines endothelial responsiveness to CD40L and permeability for leukocyte adhesion.
- **Activity of metalloproteinases (e.g., ADAM-10 / ADAM-17):** regulates CD40L shedding and generation of soluble CD40L (sCD40L).
- **Circulating sCD40L levels and clearance rate:** affect systemic proinflammatory and prothrombotic signaling.
- **Immune cell regulation (Tregs, T cells, dendritic cells):** modulates balance between pro- and anti-inflammatory pathways.
- **Cell-specific TRAF signaling intensity:** cell-dependent expression of TRAF-2 / TRAF-6 determines downstream pathway activation.
- **Phenotype of vascular wall cells (endothelial and smooth muscle cells):** influences cellular sensitivity to CD40L-mediated signaling.

Table 2. Integrative Summary: Effects of Platelet CD40L on Major Atherogenic Pathways

Pathway / Process	CD40L Influence	Consequences for Atherogenesis / Thromboatherothrombosis
Endothelial activation	Enhances via CD40 → ↑ adhesion molecules, chemokines, ROS	Promotes leukocyte recruitment and endothelial injury
Monocyte recruitment / transmigration	Through CCL2 / VCAM-1 / ICAM-1 upregulation	Increases monocyte infiltration into the intima
Macrophage / monocyte activation	Via NF-κB and tissue factor pathways	Amplifies proinflammatory and procoagulant responses
Platelet aggregation / thrombus stability	Strengthens aggregation and stabilizes thrombus formation	Facilitates thromboatherothrombotic events
Platelet–leukocyte aggregate formation	Increases aggregate number and persistence	Enhances leukocyte activation and endothelial interactions
Immunomodulation (Tregs)	Reduces regulatory T-cell populations	Decreases immune tolerance, shifting balance toward inflammation

Interpretation:

Collectively, these findings highlight the multidimensional role of platelet-derived CD40L as an amplifier of cross-talk between thrombotic and immune mechanisms within the vascular microenvironment. Its actions bridge hemostasis and inflammation, positioning CD40L as a pivotal mediator of *thrombo-inflammatory* pathology in atherosclerosis.

DISCUSSION

CD40L as a Molecular Bridge Between Thrombosis and Inflammation

Taken together, the findings discussed above emphasize that platelet-derived CD40L functions as a unique *molecular bridge* linking platelet activation to the initiation of immune and inflammatory responses. Unlike classical platelet mediators that primarily regulate aggregation and coagulation, CD40L directly activates leukocytes and vascular cells through CD40-dependent signaling pathways. This supports the evolving concept of *thromboinflammation*, in which thrombosis and inflammation act as mutually reinforcing processes, particularly within the atherosclerotic vascular microenvironment.

Context-Dependent Effects and Functional Constraints

Nevertheless, the evidence also indicates that the role of platelet CD40L is highly context-dependent. As noted previously, selective deletion of CD40L in platelets (using Pf4-Cre models) does not consistently reduce the overall size of atherosclerotic plaques but significantly decreases the incidence of thrombotic complications [Lacy et al., 2021, pp. 5–6]. This suggests that platelet CD40L primarily modulates the *complication phase* of atherosclerosis—thrombosis and neointimal remodeling—rather than the initial stages of lipid accumulation and plaque growth.

Importantly, global CD40L inhibition (not limited to platelets) has been associated with an increased risk of embolic events due to impaired thrombus stability in experimental models [Michel et al., 2017, p. 10; Lacy et al., 2021, p. 8; Cognasse et al., 2022, p. 5]. These observations underscore a major translational challenge: while CD40L represents a promising therapeutic target at the interface of thrombosis and inflammation, its systemic blockade may compromise normal hemostatic function. Therefore, future strategies should focus on **selective modulation** of CD40L–CD40 interactions—specifically those mediating pathogenic thromboinflammatory signaling—while preserving physiological platelet and vascular homeostasis.

Вот академически выверенный английский перевод этого раздела — в том же стиле, что и предыдущие части статьи (Discussion), с сохранением точных смыслов и логики:

Gaps and Outstanding Questions

Despite the extensive body of experimental research, several key areas remain insufficiently understood and warrant further investigation:

1. **Quantitative burden of CD40L / sCD40L and correlation with clinical outcomes.** Although circulating levels of soluble CD40L (sCD40L) have been measured in humans and shown to correlate with cardiovascular risk, direct evidence quantifying the *platelet-derived* contribution to total sCD40L and its relationship with atherosclerotic burden remains limited.
2. **Cellular heterogeneity of CD40L responses among platelet and leukocyte subsets.** It is possible that different platelet subpopulations (e.g., young vs. senescent platelets) vary in their responsiveness to CD40L stimulation, as well as in the expression of TRAF adapter proteins. Such heterogeneity could significantly modulate downstream inflammatory and thrombotic signaling.
3. **Cross-regulation with other platelet-derived mediators.** Activated platelets release multiple bioactive molecules—such as IL-1β, PF4 (CXCL4), and RANTES—that may interact with or amplify CD40L-mediated signaling. For example, platelet factor 4 (PF4) is known to associate with macrophages and promote lipid accumulation within plaques [Wang et al., 2020, p. 2]. The extent and mechanisms of such cross-talk remain poorly defined.
4. **Role of platelet CD40 as a receptor for CD40L (reverse signaling).** Platelets themselves express CD40 and may respond to CD40L stimulation, suggesting a potential *reverse signaling* loop that reinforces platelet activation [Gawaz et al., 2005, p. 3; Michel et al., 2017, p. 6]. The physiological relevance and signaling specificity of this feedback remain to be clarified.
5. **Clinical translation and human relevance.** Most current insights derive from murine or in vitro studies. There is a pressing need for well-designed translational and clinical investigations evaluating the selective inhibition of *platelet-derived CD40L* and its impact on thrombo-atherothrombotic outcomes without impairing normal hemostasis.

Potential Therapeutic Approaches

Given the dual nature of CD40L—acting both as a modulator of immune inflammation and as a mediator of platelet function—therapeutic interventions must be designed with high selectivity. Potential strategies include:

- **Monoclonal antibodies or antibody fragments** that selectively block CD40L interaction with specific receptors (e.g., CD40 on endothelial or leukocyte cells) without complete inhibition of platelet-associated CD40L.
- **Small-molecule inhibitors or synthetic peptides** that competitively interfere with CD40L binding to CD40 or to the α5β1 integrin.
- **Targeted nanoparticle delivery systems** capable of directing CD40L inhibitors specifically to sites of vascular injury or atherosclerotic plaques, thereby minimizing systemic effects on normal platelet function.
- **Modulation of metalloproteinase activity** (e.g., ADAM10 and ADAM17) to control CD40L shedding and limit the generation of soluble CD40L (sCD40L).
- **Combined anti-inflammatory approaches,** such as co-administration with IL-1β inhibitors or other cytokine-targeted agents, to achieve synergistic attenuation of vascular inflammation.

The successful implementation of these strategies will require a delicate balance between suppressing the pathological proinflammatory and prothrombotic effects of CD40L while preserving its physiological roles in normal hemostasis.

CONCLUSION

Taken together, the current body of literature demonstrates that platelet-derived CD40L is a potent modulator of vascular pathophysiology, promoting both inflammatory activation (through interactions with leukocytes, endothelial activation, and immune modulation) and enhancement of the procoagulant potential (through thrombus stabilization and activation of the tissue factor pathway). It serves as an integrative link between thrombosis and inflammation, particularly in atherosclerotic vessels.

However, the role of platelet CD40L in classical plaque growth appears to be less pronounced than its contribution to atherosclerotic complications such as thrombosis, embolism, and neointimal remodeling. Contextual factors — including lipid status, metalloproteinase activity, and the immune milieu — significantly modulate the intensity and character of CD40L-mediated effects. For translation into clinical applications, it is essential to establish quantitative correlations between plasma sCD40L levels and disease severity in humans, to explore its effects across cellular subpopulations, and to further elucidate its interactions with other platelet mediators. Equally important is the development of selective therapeutic strategies aimed at attenuating the pathological actions of CD40L while preserving its physiological roles in hemostasis.

REFERENCES

1. Antoniades, C., Bakogiannis, C., Tousoulis, D., Antonopoulos, A. S., & Stefanadis, C. (2009). *The CD40/CD40 Ligand System: Linking Inflammation with Atherothrombosis.* Journal of the American College of Cardiology, 54(8), 669–677.
2. Cognasse, F., Laradi, S., Berthelot, P., Bourlet, T., Marotte, H., & Garraud, O. (2022). *Platelets as Key Factors in Inflammation: Focus on CD40L/CD40.* Frontiers in Immunology, 13, 838702.
3. Gawaz, M., Langer, H., & May, A. E. (2005). *Platelets in inflammation and atherogenesis.* Journal of Clinical Investigation, 115(12), 3378–3384.

4. Langer, H. F., Daub, K., & Gawaz, M. (2022). *Chronic inflammation in atherosclerosis — The CD40L/CD40 axis.* Thrombosis and Haemostasis, 122(8), 1220–1232.
5. Lacy, M., Brass, L. F., & Diamond, S. L. (2021). *Cell-specific and divergent roles of the CD40L–CD40 axis in atherosclerosis.* Arteriosclerosis, Thrombosis, and Vascular Biology, 41(1), 76–89.
6. Lievens, D., Zernecke, A., Seijkens, T., Soehnlein, O., Beckers, L., Munnix, I. C. A., Wijnands, E., Goossens, P., Van Kruchten, R., Thevissen, L., Boon, L., Flavell, R. A., Noelle, R. J., Gerdes, N., Biessen, E. A., Daemen, M. J. A. P., Heemskerk, J. W. M., Weber, C., & Lutgens, E. (2010). *Platelet CD40L mediates thrombotic and inflammatory processes in atherosclerosis.* Blood, 116(20), 4317–4327.
7. Michel, N. A., Zirlik, A., & Wolf, D. (2017). *CD40L and its receptors in atherothrombosis — An update.* Frontiers in Cardiovascular Medicine, 4, 40.
8. Wang, L., Fan, J., Sun, G., & Sun, X. (2020). *Targeting platelets in atherosclerosis plaque formation.* International Journal of Molecular Sciences, 21(17), 6069.