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Release Of Cd40l Upon Platelet Activation As A Key Nexus Linking Thrombosis And Inflammation. Literature Review

Ruziyev Zarif Muxammadovich

https://orcid.org/0009-0009-3541-4725
Email: ruziyev.zarif@bsmi.uz
Assistant of the Department of Hematology and Clinical Laboratory Diagnostics, Bukhara State Medical Institute.
Uzbekistan, Bukhara, st. A. Navoi. 1 Tel: +998 (65) 223-00-50 e-mail: info@bsmi.uz

ABSTRACT: *Platelets, traditionally viewed as mediators of hemostasis and thrombosis, are increasingly recognized as active participants in inflammation and immunity. A central molecular link between platelet activation and inflammatory signaling is the rapid mobilization and shedding of CD40 ligand (CD40L, also known as CD154). Upon platelet activation, membrane-bound CD40L is translocated from α-granule stores to the platelet surface and then cleaved to generate soluble CD40L (sCD40L). This released CD40L can bind to a variety of receptors on endothelial cells, leukocytes, and even platelets themselves, triggering proinflammatory responses, leukocyte recruitment, and further platelet activation. In this review, we survey the literature on the mechanisms of CD40L release from platelets, the downstream signaling pathways and cellular targets, and the evidence linking CD40L to thromboinflammatory pathologies. We also discuss conceptual models that place platelet CD40L release as a "bridge" between thrombosis and inflammation. We propose a unified framework and highlight gaps for future investigation.*

Keywords: platelet activation, CD40 ligand, soluble CD40L, thrombosis, inflammation, platelet–leukocyte interactions.

INTRODUCTION

Platelets are small, anucleate cell fragments derived from megakaryocytes, whose canonical function is to maintain vascular integrity and promote clot formation upon vascular injury. However, mounting evidence over the past two decades has broadened our view of platelets as immunomodulatory and inflammatory effector cells [Platelet CD40L at the interface of adaptive immunity, 2011, p. …; Platelets as Key Factors in Inflammation, 2022, p. …]. The molecular mechanisms by which platelets influence inflammation overlap with their hemostatic machinery. Among these, the **release of CD40 ligand (CD40L, also referred to as CD154)** upon platelet activation has emerged as a compelling molecular mediator that links thrombosis and inflammation.

CD40L is a member of the tumor necrosis factor (TNF) superfamily, initially described in T-lymphocytes, where it functions in B cell help and adaptive immunity. Its expression on platelets was a surprising discovery, but subsequent studies have shown that platelets store preformed CD40L that can be rapidly mobilized to the surface and then shed as a biologically active soluble form (sCD40L) [The Signaling Role of CD40 Ligand in Platelet Biology, 2014, p. …]. Because more than 95 % of circulating CD40L originates from platelets in healthy individuals, platelet activation is the dominant source of sCD40L in many pathologies [Platelet-Derived CD40L, 2002, p. …].

The fact that CD40L engages receptors on endothelial cells, leukocytes, and platelets themselves implicates it in a wide array of processes: endothelial activation, cytokine and chemokine induction, leukocyte adhesion, platelet–leukocyte aggregates, and propagation of thrombosis under inflammatory conditions. In diseases such as atherosclerosis, acute coronary syndromes, ischemia–reperfusion injury, and autoimmune vascular disorders, the interplay between platelet activation and inflammation is believed to be critical.

This review aims to synthesize current knowledge on the mechanisms of platelet CD40L release, the downstream signaling circuits, and how these processes functionally link thrombotic and inflammatory pathways. In the "Results" section we present summary tables and conceptual schematics that consolidate findings from multiple experimental systems. We conclude by proposing conceptual models and outlining future directions for investigation.

LITERATURE REVIEW

1. Biochemistry and molecular biology of CD40L

CD40L is a type II transmembrane protein (~33 kDa) of the TNF superfamily, with a short cytoplasmic tail, a transmembrane domain, and an extracellular domain that forms homotrimers [The Signaling Role of CD40 Ligand in Platelet Biology, 2014, p. …]. On the cell surface (e.g., T cells or platelets), CD40L acts in its membrane-bound trimeric form to bind CD40 on target cells, and it can also be proteolytically cleaved to yield soluble CD40L (sCD40L). The trimeric conformation is often preserved in soluble form, and multimerization is critical for receptor engagement and signaling [The Signaling Role of CD40 Ligand in Platelet Biology, 2014, p. …].

Polymorphisms and regulatory elements in the CD40LG gene may influence expression levels and disease susceptibility, but in platelets the preformed reservoir dominates acute release responses [The Signaling Role of CD40 Ligand in Platelet Biology, 2014, p. …].

2. Storage, mobilization, and shedding of CD40L in platelets

In resting platelets, CD40L is stored intracellularly, primarily in α-granules (and possibly in less well characterized compartments) rather than on the membrane surface [The Signaling Role of CD40 Ligand in Platelet Biology, 2014, p. …]. Upon activation (e.g., by thrombin, collagen, ADP), platelets undergo degranulation and membrane trafficking events that translocate CD40L to the plasma membrane [Activated platelets rapidly up-regulate CD40L, 2004, p. …].

Once on the surface, CD40L is subject to proteolytic cleavage (shedding), generating soluble CD40L (sCD40L) that can diffuse or act locally. The kinetics of shedding and the contributing proteases vary with context, but in platelets, matrix metalloproteinases (especially MMP-2) and ADAM family proteases are implicated. Notably, the integrin αIIbβ3 may be functionally required for optimal shedding [The Signaling Role of CD40 Ligand in Platelet Biology, 2014, p. …]. In pathological states such as sepsis, MMP-9 has also been implicated in enhanced shedding [The Signaling Role of CD40 Ligand in Platelet Biology, 2014, p. …].

The regulation of CD40L mobilization and shedding involves signaling cascades, SNARE machinery (e.g. SNAP23), MAPK and NF-κB pathways, and cross talk with integrin signaling—suggesting that CD40L mobilization is integrated with platelet activation programs [The Signaling Role of CD40 Ligand in Platelet Biology, 2014, p. …]. A schematic overview is shown in published models (see Figure above) [The Signaling Role of CD40 Ligand in Platelet Biology, 2014].

3. Receptors for CD40L and binding partners

CD40L binds primarily to CD40, a TNF receptor superfamily member expressed on many cell types (e.g. endothelial cells, monocytes, macrophages, dendritic cells). In addition, CD40L can bind to integrins such as α5β1 and, in some contexts, αIIbβ3 (on platelets) via a KGD motif [Wikipedia: CD154; Soluble CD40 ligand induces β3 integrin tyrosine, 2003, p. …]. The binding to platelet integrin αIIbβ3 can act as an autocrine agonist in some systems [Prasad et al., 2003, p. …].

Platelets themselves constitutively express CD40, enabling autocrine or paracrine signaling loops via CD40L–CD40 within platelet populations [CD40 Is Constitutively Expressed on Platelets, 2002, p. …]. This receptor diversity allows CD40L to influence multiple cellular targets beyond classical immune cells.

4. Downstream signaling triggered by CD40L in diverse cells

4.1 Platelet signaling

Binding of CD40L to platelet CD40 triggers activation of NF-κB and primes platelets to respond more robustly to subsequent agonists (e.g. stronger aggregation, granule release) [CD40L Priming of Platelets via NF-κB Activation, 2018, p. …]. This autocrine loop may thus amplify platelet reactivity in inflamed or thrombogenic settings.

4.2 Endothelial cells

Endothelial cell CD40 engagement by sCD40L or platelet-bound CD40L leads to proinflammatory gene expression: induction of adhesion molecules (ICAM-1, VCAM-1, E-selectin), secretion of chemokines (IL-8, MCP-1), and release of tissue factor and reactive oxygen species (ROS) [Platelets as Key Factors in Inflammation, 2022, p. …; The inflammatory action of CD40 ligand, 1999, p. …; Platelet CD40L at the interface of adaptive immunity, 2011, p. …]. Thus platelet CD40L can convert otherwise quiescent endothelium into an activated, prothrombotic/inflammatory phenotype.

4.3 Leukocytes and monocytes

Platelet CD40L–CD40 interactions facilitate the formation of platelet–leukocyte aggregates (PLAs), boosting leukocyte adhesion, chemokine secretion (e.g. IL-1β, CCL2, CCL5), and integrin activation on neutrophils [Platelet CD40L mediates thrombotic and inflammatory processes, 2010, p. …]. These platelet–leukocyte conjugates tether to endothelial cells with higher avidity than free leukocytes, enhancing recruitment under flow [Platelet CD40L mediates thrombotic and inflammatory processes, 2010, p. …; Role of platelet biomarkers in inflammatory response, 2020, p. …]. Through CD40 engagement, monocytes and macrophages may also upregulate inflammatory cytokines.

5. Evidence linking platelet CD40L / sCD40L to thromboinflammatory disease

5.1 Observational associations

Elevated plasma sCD40L levels have been observed in cardiovascular disease, acute coronary syndrome, stroke, and autoimmune vascular diseases. Because platelets are the major source of sCD40L, such associations implicate platelet activation in these conditions [Platelet-Derived CD40L, 2002, p. …; Platelets as Key Factors in Inflammation, 2022, p. …].

5.2 Experimental and interventional studies

Blocking CD40L or CD40 in animal models often attenuates vascular inflammation, thrombus growth, and leukocyte infiltration, supporting a causal role for CD40L. For example, in models of TRALI (transfusion-related acute lung injury), anti-CD40L antibodies mitigate injury related to CD40L–CD40 activity [Platelets as Key Factors in Inflammation, 2022, p. …]. In cardiopulmonary bypass procedures, platelet activation releases sCD40L; blockade of integrin GPIIb/IIIa or P2Y12 reduces sCD40L release and downstream inflammatory responses [Cardiopulmonary Bypass Induces Release of Soluble CD40 Ligand, 2002, p. …].

In murine atherosclerosis models, repeated infusion of activated platelets accelerates lesion formation via endothelial activation and PLA formation, and this effect is attenuated when platelet CD40L is genetically deleted or neutralized [Platelet CD40L mediates thrombotic and inflammatory processes, 2010, p. …].

Other investigative studies show that exogenous sCD40L can stabilize thrombi, promote platelet aggregation, and stimulate further platelet degranulation [Platelet-Derived CD40L, 2002, p. …]. The KGD motif of sCD40L interacts with αIIbβ3 and can induce integrin signaling [Prasad et al., 2003, p. …].

Collectively, this body of evidence supports a model in which platelet CD40L release is central to amplifying both thrombosis and inflammation in vascular pathology.

DISCUSSION

Conceptual model: CD40L release as a “thromboinflammatory hub”

From the literature, one can distill a conceptual model in which platelet activation triggers a cascade:

1. **Primary activation**: vascular injury, shear stress, or agonists (thrombin, collagen, ADP) activate platelets.
2. **CD40L mobilization**: internal CD40L is trafficked to the platelet surface.
3. **Shedding / release**: membrane CD40L is cleaved to produce sCD40L; some remains membrane-bound.
4. **Paracrine / autocrine signaling**:
   a. sCD40L (and membrane CD40L) engages endothelial CD40 → endothelial activation, adhesion molecule and chemokine expression, tissue factor upregulation.
   b. sCD40L or platelet-bound CD40L engages leukocyte CD40 or integrins → platelet–leukocyte aggregation, leukocyte activation, cytokine release.
   c. CD40L engages platelet CD40 or integrin, amplifying platelet responsiveness.
5. **Reinforcement**: positive feedback loops sustain further platelet activation, leukocyte recruitment, and localized inflammation, bridging thrombosis and immune response.

In this model, CD40L acts as a **nexus** that communicates the platelet activation state to vascular and immune cells, thereby linking coagulation to inflammation.

Strengths, caveats, and unresolved issues

This model is supported by a robust body of in vitro, ex vivo, and in vivo evidence. The observations that blocking CD40L/CD40 attenuates vascular inflammation, that sCD40L levels correlate with cardiovascular risk, and that platelet CD40L is abundant make this a compelling mechanistic axis.

However, several caveats and gaps remain:

- The kinetics and locality of CD40L release: under high shear or in microcirculation, how far does sCD40L diffuse, and how effectively is it captured by local endothelial or leukocyte receptors?
- Specific contributions of membrane vs. soluble CD40L: in many experiments, one cannot distinguish which form mediates which effect.

- Redundancy with other platelet inflammatory mediators: platelets also release chemokines, cytokines, and microvesicles; the relative weight of CD40L's contribution is uncertain.
- Context dependence: different vascular beds (arterial vs venous), inflammatory milieus, or disease states may modulate the relevance of CD40L.
- Therapeutic targeting: direct CD40L or CD40 blockade has encountered complications such as thrombocytopenia or adverse immune effects, highlighting the need for precision in therapeutic intervention [The Double-Edged Sword of Platelet CD40L, 2021, p. …].
- Quantitative modeling is lacking: how many molecules of sCD40L are needed to trigger endothelial activation under physiological flow?

Potential implications and translational prospects

If platelet CD40L release is indeed a central mediator of thromboinflammatory crosstalk, then interventions aimed at reducing CD40L shedding (e.g. inhibiting specific MMPs or ADAM proteases), blocking CD40L interactions locally, or modulating platelet preactivation states could attenuate vascular inflammation without completely impairing hemostasis. Emerging antiplatelet strategies that more selectively modulate platelet inflammatory mediator release (rather than grossly suppressing aggregation) are of particular translational interest [Targeting platelet-derived soluble CD40 ligand, 2013, p. …].

Furthermore, measurement of platelet-derived sCD40L might serve as a biomarker bridging thrombotic risk with vascular inflammation in clinical settings.

RESULTS

Although this is a review article, we present here two schematic summaries and a hypothetical summary table that synthesize key empirical findings from the literature.

Table 1. Summary of key experimental findings on platelet CD40L release and downstream effects

Study / System	Platelet Activation & CD40L Release	Downstream Effects Observed	Intervention / Blockade Effects
Henn et al. (Circulation)	Platelets rapidly express surface CD40L and shed sCD40L upon activation	sCD40L induces endothelial cells to express adhesion molecules, chemokines, and MMPs	Blocking CD40L reduces endothelial activation [Platelet-Derived CD40L, 2002, p. …]
Urbich et al. / others	Platelet infusion in Apoe$^{-/-}$ mice	Accelerated atherosclerosis, increased endothelial activation and leukocyte adhesion	Genetic deletion or blockade of platelet CD40L attenuates lesion progression [Platelet CD40L mediates thrombotic and inflammatory processes, 2010, p. …]
CPB (cardiopulmonary bypass) clinical setting	CPB induces release of sCD40L from platelets	Correlated inflammatory and thrombotic complications	GPIIb/IIIa or P2Y12 blockade reduces sCD40L and inflammation [Cardiopulmonary Bypass Induces Release of Soluble CD40 Ligand, 2002, p. …]
Prasad et al. (PNAS)	Exogenous sCD40L binding to αIIbβ3	Tyrosine phosphorylation of β3, platelet activation	Inhibition of integrin binding abolishes effect [Prasad et al., 2003, p. …]
CD40L priming study	CD40L engagement triggers NF-κB in platelets	Enhanced response to subsequent agonists	CD40 neutralization reduces priming effect [CD40L Priming of Platelets via NF-κB Activation, 2018, p. …]

(Note: the page citations are representative and should be refined to match your final reference list.)

Figure 1 (schematic). Cascade of platelet CD40L mobilization and signaling

Below is a conceptual schematic (adapted from published diagrams) illustrating the successive steps in platelet CD40L mobilization, shedding, and downstream interactions:

1. Platelet activation via agonists →
2. Membrane trafficking and presentation of CD40L →
3. Shedding of sCD40L via proteases (e.g. MMP-2, ADAMs) →
4. Binding of sCD40L / platelet CD40L to endothelial CD40 → endothelial activation →
5. Engagement of leukocyte CD40 / integrins → PLA formation, leukocyte activation →
6. Autocrine platelet CD40/CD40L signaling → amplification

(You can redraw or refine this schematic according to your design preferences; possible topologies include positive feedback loops and cross-cellular arrows.)

Figure 2 (schematic). Platelet–leukocyte–endothelial cross talk mediated by CD40L

This second schematic illustrates cellular interactions in a vascular microenvironment:

- Activated platelet displays CD40L and releases sCD40L.
- Endothelial cell receives CD40L signal → upregulates adhesion molecules (ICAM, VCAM), chemokines, tissue factor.
- Leukocytes adhere via P-selectin, form PLAs, receive further activation via CD40.
- Platelets and leukocytes act in concert to propagate local inflammation and thrombosis.

These summary visuals synthesize findings from multiple studies and help unify understanding of the complex cross talk implicit in CD40L-mediated signaling.

CONCLUSION

The release of CD40L from activated platelets constitutes a mechanistic linchpin connecting thrombosis and inflammation. Through mobilization from α-granules, shedding into soluble form, and binding to diverse receptors on endothelium, leukocytes, and platelets themselves, CD40L operates as a molecular messenger that translates platelet activation into inflammatory signals. The literature supports a model in which CD40L functions as a **thromboinflammatory hub**—amplifying platelet reactivity, initiating endothelial activation, and recruiting leukocytes via platelet–leukocyte aggregates.

Despite the depth of insight accrued, several open questions persist: the spatial and temporal dynamics of CD40L diffusion under flow, the relative contributions of membrane vs soluble CD40L in vivo, precise quantitative thresholds for signaling activation, and the interplay of CD40L with other platelet inflammatory mediators. From a translational standpoint, modulating CD40L release or signaling holds promise for attenuating vascular inflammation without broadly suppressing hemostasis—but such approaches will require careful balancing to avoid adverse immunological consequences.

Going forward, integrating quantitative modeling, high-resolution imaging of thrombosis/inflammation in vivo, and refined molecular targeting of CD40L pathways may clarify the roles and therapeutic potential of this axis.

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