Review Article

Revisiting the Platelet–β-Cell Axis: Insights into How Platelet-Derived Mediators, Lipid Signaling, and DOC2B Pathways Converge to Drive β-Cell Dysfunction in Type 2 Diabetes

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Abstract

Type 2 diabetes mellitus (T2DM) is a multifactorial disorder where platelet-derived mediators, lipid metabolic pathways, and exocytotic proteins intersect to drive β-cell dysfunction. Activated platelets release serotonin, platelet factor 4 (PF4), sphingosine-1-phosphate (S1P), and microvesicles that trigger oxidative and endoplasmic reticulum (ER) stress in pancreatic islets. CD36-mediated lipid uptake and sphingolipid imbalance intensify ceramide-driven mitochondrial damage. These insults converge on exocytotic failure through disruption of DOC2B, a Ca^{2+}-sensitive mediator of insulin vesicle fusion. Revisiting this axis clarifies how thromboinflammation and lipotoxicity orchestrate β-cell failure and highlights emerging therapeutic targets for T2DM. This review introduces a novel integrative perspective linking platelet-derived mediators, lipid dysregulation, and DOC2B-mediated exocytotic failure as a unified model of β-cell dysfunction in T2DM.

Background and Rationale

Type 2 diabetes mellitus (T2DM) is not solely a metabolic disease but also a vascular-inflammatory disorder [1–4]. Platelets in T2DM exhibit hyperactivity and release mediators capable of influencing β-cell function and viability [9–17]. This concept has evolved into the platelet–β-cell axis, a bidirectional pathway linking thromboinflammation to insulin secretion defects. The diversity of platelet mediators-PF4, serotonin, S1P, and platelet-derived microvesicles-illustrates how hemostatic cells can influence pancreatic islets beyond coagulation. Although previous studies have recognized platelet–β-cell crosstalk in the context of inflammation, oxidative stress, and lipid overload, none have comprehensively integrated the DOC2B-mediated exocytotic machinery with platelet-derived lipid signaling and CD36-driven lipotoxic stress as a unified mechanism of β-cell failure. This review introduces a novel tri-axis model-encompassing platelet mediators, lipid dysregulation, and DOC2B dysfunction-that provides a systems-level explanation of how thromboinflammatory and lipotoxic pathways converge to precipitate β-cell demise in T2DM.

Table 1: Summary of Platelet-Derived Mediators Involved in β-Cell Dysfunction.

Platelet Mediator	Main β-Cell Target	Molecular Effect	Key Mechanism	References
Platelet Factor 4 (PF4)	Heparan sulfate receptor on β-cell membrane	Increases intracellular Ca^{2+} and ROS via NADPH oxidase activation	Induces oxidative stress and impairs insulin gene transcription	[11, 14, 15, 17]
Serotonin (5-HT)	5-HT_2B receptor on β-cells	Stimulates acute insulin exocytosis; chronic exposure causes desensitization	Protein serotonylation of SNARE components	[11, 37]
Sphingosine-1-Phosphate (S1P)	S1PR2/S1PR3 receptors	Regulates Ca^{2+} signaling and mitochondrial activity; protective at physiological levels, toxic when excessive	Ceramide–S1P rheostat in β-cell survival	[6, 7, 31, 38]
Platelet Microvesicles (PMVs)	β-cell cytoplasm and islet endothelium	Transfer lipids and miRNAs; induce ER stress and inflammation	Vesicular crosstalk between platelet and islet cells	[18, 33]
Platelet-Derived ROS	β-cell mitochondria	Oxidizes DOC2B and impairs vesicular fusion	NOX2/NOX4-mediated chronic oxidative stress	[34, 36, 40]

Of note, the clinical relevance of platelet hyperactivity in T2DM extends beyond hemostasis. Several population-based analyses demonstrate that abnormal platelet indices-such as mean platelet volume and platelet distribution width-correlate strongly with metabolic control and the development of microvascular complications [9,10,11,13,15]. Such platelet activation is closely related to systemic inflammation and oxidative imbalance, both of which accelerate β-cell exhaustion and insulin secretory decline [14,16,17]. These findings support the notion that platelet dysfunction may precede overt hyperglycemia and serve as an early biomarker of metabolic deterioration [11,13,17]. Collectively, these insights strengthen the hypothesis that the platelet–β-cell axis represents a pivotal link between vascular inflammation and endocrine dysregulation in T2DM pathogenesis [9–17].

Platelet Activation and Thromboinflammatory Mediators

Activated platelets in T2DM release a complex repertoire of cytokines, lipid messengers, and extracellular vesicles. PF4 and serotonin stimulate intracellular Ca^{2+} signaling and oxidative stress, while platelet-derived microvesicles (PMVs) deliver ceramides and miRNAs that impair insulin gene expression [11,14,16–18,33]. PMV-induced activation of NADPH oxidase (NO X 2/4) creates persistent ROS that propagates ER stress and apoptosis.

Lipid Signaling: CD36 and Sphingolipid Dysregulation

CD36 acts as a lipid gatekeeper for long-chain fatty acids and oxidized LDL. Its overactivation in β-cells promotes ceramide accumulation and mitochondrial ROS production [5,30,32]. Simultaneously, sphingolipid imbalance-especially elevated ceramide and diminished S1P-drives ER stress and apoptosis [6–8,31,38].

CD36 serves as a metabolic gatekeeper that facilitates the

uptake of long-chain fatty acids and oxidized lipoproteins into β-cells. While transient activation of CD36 supports membrane remodeling and energy supply for insulin secretion, chronic overexpression under hyperglycemic and lipotoxic conditions drives excessive fatty acid influx, ceramide accumulation, and reactive oxygen species (ROS) generation [5, 30, 32]. This oxidative and ER stress environment disrupts mitochondrial respiration and promotes apoptotic cascades, contributing directly to β-cell dysfunction [31, 38].

In parallel, sphingolipid metabolism-particularly through sphingosine-1-phosphate (S1P) and ceramide-plays a dual role in maintaining β-cell integrity. Physiological S1P signaling via S1PR2 and S1PR3 supports insulin secretion and cellular resilience; however, imbalance in the ceramide/S1P ratio shifts the intracellular milieu toward apoptosis and inflammation [6, 7, 31, 38]. Activation of neutral sphingomyelinase-2 (nSMase2) under hyperglycemic conditions further amplifies ceramide production, establishing a self-perpetuating cycle of lipotoxic stress.

Taken together, aberrant CD36 signaling and sphingolipid dysregulation form a lipid-centric framework of β-cell injury that intertwines metabolic overload with oxidative stress. Importantly, these lipid pathways also sensitize β-cells to platelet-derived mediators-such as S1P and microvesicle lipids-linking lipid metabolism to thromboinflammatory crosstalk within the platelet–β-cell axis [6, 7, 18, 30–33, 38]

This integrative lipidomic dysfunction couples metabolic overload with platelet activation, reinforcing the feed-forward cycle of inflammation and β-cell failure.

Table 2: Relationship between CD36 and Sphingolipid Pathways in β-Cell Dysfunction.

Lipid Pathway	Core Components	Effect on β-Cells	Mechanistic Evidence	References
CD36-mediated lipid uptake	CD36, oxidized LDL, long-chain fatty acids	Ceramide accumulation, ROS generation, apoptosis	CD36 overexpression triggers mitochondrial and ER stress	[5, 30, 32]
Ceramide synthesis pathway	Neutral sphingomyelinase-2 (nSMase2), serine palmitoyl transferase	Activates caspase-3, CHOP, and suppresses GSIS	Ceramide inhibits SNARE complex assembly	[6, 7, 31, 38]
S1P signaling	S1PR2/S1PR3	Maintains cell survival at moderate levels, pro-apoptotic when excessive	Regulates balance between β-cell proliferation and apoptosis	[6, 31, 38]
Lipid vesicle crosstalk	Platelet-derived microvesicles	Transfers ceramide and inflammatory lipids to β-cells	Mediates intercellular lipotoxicity via vesicle transport	[18, 28, 33]

DOC2B and Exocytotic Failure

DOC2B (Double C2-like Domain β) is a calcium-sensitive protein critical for insulin granule fusion. Under oxidative and nitrosative stress, DOC2B undergoes conformational changes and post-translational modifications that impair its SNARE interaction [29,35,40]. Ceramide accumulation and ROS from platelet activity synergistically reduce DOC2B stability, leading to defective glucose-stimulated insulin secretion (GSIS). DOC2B (Double C2-like Domain β) serves as a critical Ca^{2+} sensor that regulates insulin granule fusion with the plasma membrane. Functionally, it bridges glucose-induced Ca^{2+} influx to the SNARE complex-comprising syntaxin-1A, SNAP-25, and VAMP2-to ensure the timing and efficiency of insulin release [29, 35]. In healthy β-cells, rapid DOC2B phosphorylation at tyrosine residues enables synchronous exocytosis during the first-phase glucose-stimulated insulin secretion (GSIS). However, diabetic stressors-such as ROS accumulation and S-nitrosylation-induce structural alterations that weaken DOC2B–SNARE interactions, resulting in delayed or incomplete vesicle fusion [34, 36, 40].

Beyond its exocytotic function, DOC2B also modulates cytoskeletal rearrangement and vesicle trafficking, processes that depend on balanced redox signaling. Ceramide-mediated proteasomal degradation and endoplasmic-reticulum stress markedly decrease DOC2B expression, linking lipid overload to secretory insufficiency [31, 38]. Interestingly, recent evidence shows that β-cells under metabolic stress can release DOC2B within extracellular vesicles, suggesting a potential adaptive or compensatory mechanism and a measurable biomarker of β-cell distress [29].

Taken together, these findings position DOC2B as a convergence point where oxidative, nitrosative, and lipotoxic stress intersect to impair insulin exocytosis. Targeting post-translational regulation of DOC2B-by preventing S-nitrosylation, enhancing phosphorylation, or stabilizing its protein structure-may represent a promising strategy to restore β-cell secretory competence [29, 35, 36, 40].

Table 3: Molecular Links between Oxidative Stress and Impaired Insulin Exocytosis via DOC2B.

Mediator / Pathway	Effect on DOC2B	Impact on Insulin Secretion	References
ROS (NOX2/NOX4)	Oxidation of cysteine residues in DOC2B	Weakens SNARE complex binding	[36]
S-nitrosylation	Modification of tyrosine residues in DOC2B	Disrupts vesicle docking and exocytosis	[40]
Ceramide	Promotes proteasomal degradation of DOC2B	Reduces GSIS and granule stability	[31, 38]
Loss of tyrosine phosphorylation	Inactivates DOC2B	Impairs insulin granule fusion and release	[35]
Extracellular vesicle export	Induces DOC2B secretion into plasma vesicles	Serves as a marker of β-cell stress	[29]

Interestingly, DOC2B acts as a calcium sensor that interacts dynamically with syntaxin-1A, Munc18-1, and SNAP25 to fine-tune the timing and amplitude of insulin vesicle release [35]. Under physiologic conditions, Ca^{2+} influx triggers conformational changes within its tandem C2 domains, ensuring synchronized glucose-stimulated insulin secretion (GSIS) [29,35]. However, oxidative stress and nitrosative modifications (such as S-nitrosylation of tyrosine residues) disrupt DOC2B conformation and its binding to SNARE proteins, resulting in asynchronous vesicle docking and diminished first-phase insulin secretion [34,36,40]. Lipid-induced ceramide accumulation and proteasomal degradation further exacerbate DOC2B loss, forming a mechanistic bridge between lipotoxicity and exocytotic failure [31,38]. These molecular events not only explain the blunted GSIS observed in T2DM but also highlight DOC2B as a promising therapeutic checkpoint to restore β-cell competency [29,35,40].

Integrative Mechanism

The Platelet–β-Cell Axis Revisited

This section introduces the novel integrative model proposed in this review, which unifies platelet activation, lipid dysregulation, and DOC2B exocytotic failure into a single mechanistic framework. This conceptual triad has not been previously described in existing platelet or β-cell literature.

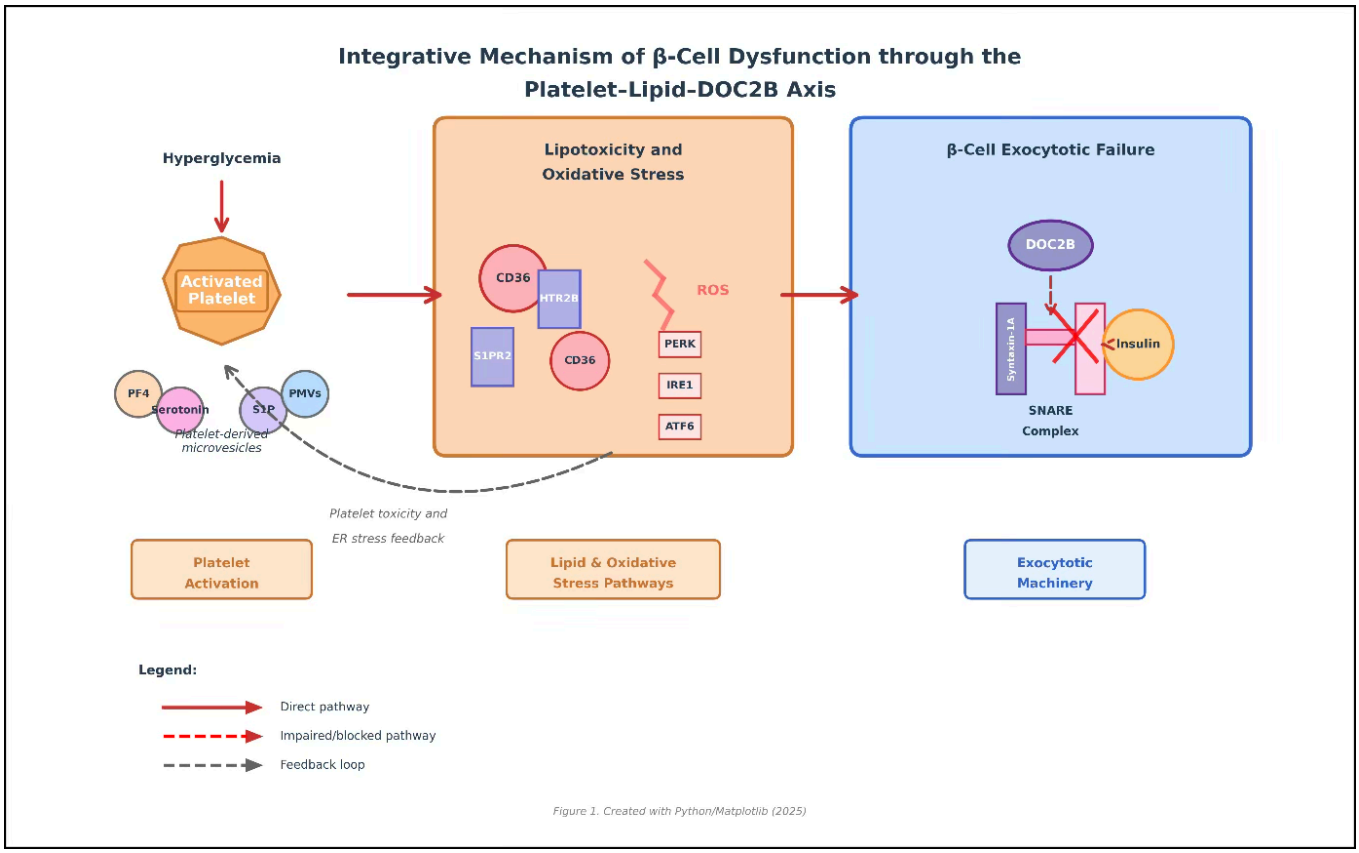
The platelet–β-cell axis can be visualized as a unified network: platelet activation → release of mediators (PF4, S1P, PMVs) → CD36/nSMase-2-driven ceramide accumulation → ROS/ER-stress-mediated DOC2B dysfunction → insulin exocytosis failure → hyperglycemia → further platelet activation [5–8,11–18,28–36,38–40].

The illustration should display three interconnected modules:

1. Activated Platelets (releasing PF4, S1P, serotonin, PMVs)
2. Lipotoxic Pathway (CD36, ceramide, NOX2/4, ER stress)
3. Exocytotic Machinery (DOC2B, SNARE, Insulin Vesicle)

Arrows between modules represent the self-reinforcing loop from metabolic overload to β-cell demise.

Figure 1: Integrative Mechanism of β-Cell Dysfunction through the Platelet–Lipid–DOC^{2}BAxis Created with BioRender.com (accessed 2025).



Clinical and Translational Implications

Therapeutically, targeting the platelet–β-cell axis could complement glucose-centric care. Antiplatelet agents, CD36 inhibitors, sphingolipid modulators, and DOC2B-stabilizing compounds hold potential to restore β-cell integrity [5,11–17,30–32,35,38–40]. Circulating biomarkers such as platelet microvesicles, sphingolipid ratios, and soluble DOC2B warrant further evaluation as indicators of β-cell stress and treatment response.

Beyond pharmacologic modulation, integrating platelet and lipid biomarkers into metabolic screening may refine early detection of β-cell deterioration. Combined assessment of circulating platelet-derived vesicles, ceramide/S1P ratios, and soluble DOC2B levels could identify subclinical β-cell stress before overt hyperglycemia manifests [18,28,31,33]. Furthermore, experimental models demonstrate that simultaneous targeting of platelet activation, CD36-mediated lipid uptake, and sphingolipid imbalance can synergistically preserve insulin secretion and metabolic stability [5,6,30–32]. In particular, S1P receptor modulators, ceramide synthesis inhibitors, and CD36 antagonists are emerging as novel adjuncts to glucose-lowering therapy [6,7,31,38]. Translating these mechanistic insights into clinical practice could open new therapeutic avenues by attenuating platelet-driven oxidative stress and maintaining DOC2B functionality [11,15,29,35,40].

Conclusion and Future Perspectives

Revisiting the platelet–β-cell axis highlights an underappreciated dimension of metabolic crosstalk in type 2 diabetes mellitus, where thromboinflammatory signaling, lipid imbalance, and vesicular exocytotic failure act in concert to drive β-cell demise. This integrative model not only bridges vascular and endocrine pathology but also reframes diabetes as a disorder of intercellular communication rather than isolated metabolic dysfunction. Future investigations should employ longitudinal platelet transcriptomic and lipidomic profiling alongside molecular indices of β-cell exocytosis-such as DOC2B, SNARE integrity, and ceramide/S1P ratios-to delineate temporal disease trajectories and reveal precision-targetable pathways [1, 5–7, 11–12, 20–22, 28–31, 34–36, 38–40].

Ultimately, translating these mechanistic insights into clinical practice could yield novel biomarkers for early detection and therapeutic strategies aimed at restoring β-cell resilience through modulation of platelet and lipid signaling networks. In conclusion, our review contributes a new conceptual understanding by framing T2DM as a disorder of intercellular communication, in which platelet-derived mediators, lipid metabolic stress, and DOC2B dysfunction act synergistically. This integrative approach not only connects vascular and endocrine pathology but also establishes a mechanistic bridge

that may guide the development of platelet-targeted and DOC2B-modulating therapies.

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Ethics Statement
This article is narrative review based entirely on previously published research and publicly available data. No. new studies involving human participants or animals were conducted by the authors. Therefore,ethical approval and informed consent were not required. All original sources were appropriately cited to maintain academic integrity and to acknowledge prior work. The review was performed in accordance with the principles and guidelines of the Committee on Publication Ethics(COPE).

Artificial Intelligence (AI) Assistance Declaration
ChatGPT (OpenAI, GPT-5) was used to support linguistic refinement, structural formatting, and reference alignment in this manuscript. All conceptual ideas, data interpretation, and final conclusions are entirely the authors' own responsibility.

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