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Mini Review

Neutrophil-Derived Migrasomes: A Novel and Essential Component of the Hemostatic System

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ABSTRACT

The classical view of hemostasis centers on platelets, endothelial cells, and plasma coagulation factors. Recent research has identified neutrophil-derived migrasomes as a previously unrecognized, indispensable cellular component of the coagulation system. These migrasomes, actively shed by migrating neutrophils, function as autonomous hemostatic units. They are uniquely equipped to adsorb and concentrate key coagulation factors from plasma via a cholesterol ester-enriched membrane, and are adorned with high-affinity adhesion molecules that enable their preferential recruitment to sites of vascular injury. At the injury site, migrasomes trigger rapid platelet activation and robust clot formation. Genetic or cellular ablation of migrasomes results in severe bleeding diathesis, which can be rescued by their exogenous administration. Furthermore, their production is markedly amplified during systemic infection and inflammation, linking innate immunity to thrombosis. This mini-review synthesizes the discovery of neutrophil-derived migrasomes as essential hemostatic agents, detailing their mechanisms of action and profound implications for understanding and treating coagulation disorders.

Keywords: Migrasome; Neutrophil; Hemostasis; Coagulation; Platelet Activation; Thrombosis.

Received: Feb 01, 2026
Accepted: Apr 02, 2026
Published: Apr 03, 2026

Citation: Jiang D, Yu L, Neutrophil-Derived Migrasomes: A Novel and Essential Component of the Hemostatic System, Clin Cardiol. 2026; 6(1): 1044.

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INTRODUCTION

Hemostasis is a vital, complex physiological process that maintains blood fluidity while enabling rapid clot formation upon vascular injury. The established paradigm involves the coordinated response of the vascular endothelium, circulating platelets, and the enzymatic cascade of plasma coagulation factors [1,2.] Platelets are the primary cellular actors, adhering to exposed subendothelial matrix, activating, aggregating, and providing a catalytic surface for thrombin generation [3]. However, the observation that neutropenia or neutrophil dysfunction can lead to bleeding complications hinted at a missing component in this scheme [4].

The recent discovery of neutrophil-derived migrasomes has fundamentally expanded this paradigm [5]. Migrasomes are large, vesicular organelles that form on the retraction fibers of migrating cells and are released into the extracellular space [6-8]. While previously studied in developmental biology [6,9], and mitochondrial quality control [10], their abundance and function in the circulatory system were unknown. This review highlights the seminal work establishing circulating migrasomes, released specifically from neutrophils, as a non-redundant, essential element of the hemostatic system, operating in concert with platelets to ensure swift and

localized clot formation [5].

MIGRASOMES IN CIRCULATION: DISCOVERY AND IDENTIFICATION

Initial in vivo imaging revealed that neutrophils constitutively generate and release migrasomes into the bloodstream [10,11]. Advanced isolation techniques, combining differential centrifugation with positive (anti-Ly6G) and negative immune-selection, allowed for the purification of these structures from blood. Critically, isolated migrasomes were distinguished from neutrophil extracellular traps (NETs), microparticles, and exosomes by definitive markers, morphology (showing characteristic attached retraction fibers), and the absence of phosphatidylserine exposure. Quantification in mouse and human blood established their presence at a remarkable ratio of approximately 1 migrasome to 100-300 platelets, indicating a substantial population with potential systemic function [5].

A CATALYTIC PLATFORM FOR COAGULATION FACTORS

Proteomic analysis yielded a surprising finding: compared to platelets, purified neutrophil-derived migrasomes were extraordinarily enriched with a wide array of coagulation factors, including prothrombin, Factor X, and Factor XIII [5]. This enrichment is not due to endogenous synthesis by neutrophils, but rather to active adsorption from plasma onto the migrasome surface. The unique lipid composition of the migrasome membrane, particularly its high concentration of cholesterol esters (ChE)—a feature absent in neutrophil plasma membranes and platelets—was identified as the key determinant. In vitro reconstitution experiments with synthetic liposomes confirmed that ChE is necessary and sufficient to confer plasma coagulation factor-adsorbing capability [5]. This designates the migrasome as a mobile, pre-loaded catalytic platform, concentrating the enzymatic machinery for thrombin generation directly at its surface.

TARGETED RECRUITMENT AND SYNERGY WITH PLATELETS

For migrasomes to function in hemostasis, they must localize to injury sites. Migrasomes are enriched with integrins and other adhesion molecules, which are maintained in a high-affinity state 5. In vivo and ex vivo flow assays demonstrated that migrasomes rapidly and preferentially accumulate on exposed collagen at vascular injury sites. This targeted recruitment elevates the local migrasome-to-platelet ratio to a critical threshold (e.g., ~1:20) that triggers activation.

Upon co-localization, migrasomes potently activate platelets. In vitro, they induce strong platelet aggregation, CD62P exposure, and morphological changes exceeding those induced by thrombin alone 5. The mechanism is dual: migrasomes provide a localized, high-density source of active coagulation factors (notably thrombin), and their physical association with platelets likely creates a synergistic, integrated clotting unit. This partnership establishes a binary system: platelets provide the primary adhesive mass and structural scaffold, while migrasomes deliver a potent, localized burst of coagulant activity, ensuring a rapid and robust hemostatic response.

IN VIVO ESSENTIALITY AND PATHOPHYSIOLOGICAL IMPLICATIONS

Genetic evidence solidifies their essential role. Mice with a myeloid-specific knockout of Tspan9, a tetraspanin critical for migrasome biogenesis, have significantly reduced circulating migrasomes and exhibit a pronounced bleeding phenotype in tail-bleeding assays [5]. Crucially, this defect is rescued by intravenous infusion of wild-type migrasomes, establishing a direct causal link. This mirrors the bleeding observed upon neutrophil depletion.

The pathophysiological relevance is underscored by the finding that migrasome production is dramatically upregulated during systemic inflammation and bacterial infection [5]. This positions migrasomes as a crucial link between innate immunity and hemostasis, potentially explaining the prothrombotic state associated with severe infections and inflammatory diseases [12]. Their dysregulation may contribute to thrombosis in conditions like sepsis, while their deficiency or dysfunction could underlie certain inflammatory bleeding disorders.

CONCLUSION AND FUTURE PERSPECTIVES

The identification of neutrophil-derived migrasomes represents a paradigm shift in our understanding of hemostasis. They are not passive bystanders but essential active participants, functioning as adhesive, coagulant-rich particles that amplify and focalize the clotting response in partnership with platelets.

Stage of Hemostasis	Role of Neutrophil-Derived Migrasomes
Initiation	Preferential adhesion to exposed subendothelial collagen via high-affinity integrins.
Amplification	Provide a concentrated, membrane-bound platform of adsorbed coagulation factors.
Propagation	Generate a localized burst of thrombin, potently activating nearby platelets and fibrinogen.
Clot Stabilization	Physical integration within the platelet-fibrin meshwork.

Future research must elucidate the detailed molecular interactions between migrasomes and platelets, define their role in various thrombotic and hemorrhagic diseases, and explore their potential as therapeutic targets or diagnostic biomarkers. Modulating migrasome formation or activity could open novel avenues for antithrombotic or pro-hemostatic therapies.

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