Indonesian Journal of Health Science
Volume 6 No.1, 2026

IMMUNOTHROMBOSIS AS A BRIDGE BETWEEN INNATE IMMUNITY AND HEMOSTASIS: A NARRATIVE REVIEW OF EMERGING MECHANISMS

Anang Rizky Maulana 1); Cici Nuriah 2); Faradiyan Kencana 3)

1) anang.rizky@institutkesehatanhermina.ac.id, **Institut Kesehatan Hermina**
2) cicinuriah@gmail.com, **Institut Kesehatan Hermina**
3) faradiyankencana07@gmail.com, **Institut Kesehatan Hermina**

Abstract
Background: Immunothrombosis is an evolutionarily conserved host defense mechanism integrating innate immunity and hemostasis to limit pathogen dissemination through localized thrombus formation. While physiologically protective, dysregulated immunothrombosis contributes to thrombo-inflammatory diseases. **Objective:** This narrative review summarizes emerging cellular and molecular mechanisms linking innate immunity and coagulation, with emphasis on their pathological and therapeutic implications. **Methods:** A narrative literature review was conducted using Scopus-indexed journals retrieved from PubMed, Scopus, and ScienceDirect, prioritizing review articles and landmark original studies published between 2013 and 2025. **Results:** Immunothrombosis is orchestrated by neutrophils, platelets, monocytes, endothelial cells, and complement systems through mechanisms including neutrophil extracellular trap (NET) formation, tissue factor expression, inflammasome activation, and immune–coagulation crosstalk. **Conclusion:** Immunothrombosis represents a fundamental biological bridge between innate immunity and hemostasis, offering novel therapeutic targets in thrombo-inflammatory disorders.
Keywords: Hemostasis; Immunothrombosis; Innate immunity; NETs; Thrombo-inflammation

INTRODUCTION

Hemostasis and innate immunity are evolutionarily conserved biological systems designed to protect the host from bleeding and infection, respectively. Traditionally viewed as distinct processes, increasing evidence demonstrates extensive functional and molecular overlap between coagulation and immune responses (Engelmann & Massberg, 2013; Levi & van der Poll, 2017). This intersection has been conceptualized as immunothrombosis, a physiological mechanism whereby innate immune activation triggers localized thrombus formation to entrap and neutralize invading pathogens (Engelmann & Massberg, 2013).

Immunothrombosis differs fundamentally from pathological thrombosis, as it is spatially restricted, tightly regulated, and closely linked to antimicrobial defense (Gaertner & Massberg, 2016). Key cellular components of innate immunity, including neutrophils, monocytes, and platelets, actively participate in coagulation through the expression of tissue factor, release of procoagulant mediators, and formation of extracellular scaffolds (Iba & Levy, 2020; Nicolai & Massberg, 2020). These processes ensure pathogen containment while minimizing systemic coagulation.

However, excessive or dysregulated immunothrombosis results in widespread microvascular thrombosis, impaired tissue perfusion, and organ dysfunction, as observed in sepsis, severe viral infections, and autoimmune diseases (Delabranche et al., 2017; Aklilu et al., 2025). Understanding the mechanisms underlying immunothrombosis is therefore critical for distinguishing protective host defense from harmful thrombo-inflammatory pathology.

METHODS

This narrative review was conducted by searching PubMed, Scopus, and ScienceDirect databases for English-language articles published between 2013 and 2025. Search terms included immunothrombosis, innate immunity, hemostasis, neutrophil extracellular traps, platelets, tissue factor, and thrombo-inflammation. Priority was given to review articles and highly cited original studies published in Scopus-indexed journals. Articles were selected based on relevance to immune–coagulation interactions and emerging mechanistic insights. No formal quality appraisal was performed as this study was designed as a narrative review.

RESULTS AND DISCUSSION

The results of this narrative review are presented thematically to synthesize current evidence on the cellular and molecular mechanisms of immunothrombosis. The discussion integrates experimental and clinical findings to highlight the dual role of immunothrombosis in host defense and disease pathogenesis.

Conceptual and Evolutionary Basis of Immunothrombosis

The concept of immunothrombosis was formally introduced to describe intravascular coagulation as an effector arm of innate immunity rather than a purely pathological event (Engelmann & Massberg, 2013). From an evolutionary perspective, coagulation systems emerged not only to prevent hemorrhage but also to restrict microbial dissemination following vascular injury (Loof et al., 2018). Early multicellular organisms relied on clot formation as a primitive immune strategy, highlighting the ancient origins of immune–coagulation crosstalk (Doolittle, 2012).

In mammals, immunothrombosis operates primarily within the microvasculature, where immune cells, platelets, and endothelial cells collaborate to generate fibrin-rich thrombi at sites of infection (Gaertner & Massberg, 2016). This process is regulated by endogenous anticoagulant pathways and fibrinolysis, ensuring balance between host defense and vascular patency (Esmon, 2012).

Cellular Mechanisms of Immunothrombosis

Neutrophils and NET Formation

Neutrophils are central mediators of immunothrombosis through the release of neutrophil extracellular traps (NETs), composed of decondensed chromatin decorated with histones and antimicrobial proteins (Brinkmann et al., 2004). NETs provide a structural scaffold that promotes platelet adhesion, fibrin deposition, and red blood cell entrapment, thereby stabilizing immunothrombi (Fuchs et al., 2010).

NET formation (NETosis) is triggered by microbial products, inflammatory cytokines, and platelet–neutrophil interactions, often mediated by PAD4-dependent histone citrullination (Martinod & Wagner, 2014). While NETs enhance pathogen clearance, excessive NETosis promotes endothelial damage and thrombosis (Thålin et al., 2019).

Platelets as Immune Cells

Platelets are increasingly recognized as immune effector cells that bridge hemostasis and innate immunity (Semple et al., 2011). Beyond their classical role in clot formation, platelets express pattern recognition receptors and secrete pro-inflammatory mediators that activate leukocytes (Koupenova et al., 2018).

Platelet–neutrophil aggregates amplify NET release and tissue factor expression, reinforcing immunothrombotic responses (Clark et al., 2007). Dysregulated platelet activation contributes to thrombo-inflammatory conditions, including sepsis and viral infections (Zarbock et al., 2006).

Monocytes and Endothelial Cells

Monocytes contribute to immunothrombosis through upregulation of tissue factor in response to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (Østerud, 2012). Endothelial cells, when activated or injured, lose their anticoagulant phenotype and promote leukocyte adhesion, platelet aggregation, and coagulation (Pober & Sessa, 2007).

Molecular Pathways Linking Innate Immunity and Coagulation

Tissue Factor and Coagulation Activation

Tissue factor (TF) is a central molecular link between immunity and coagulation. TF expression on monocytes and endothelial cells initiates the extrinsic coagulation pathway, leading to thrombin generation and fibrin formation (Mackman, 2009). Inflammatory signaling via toll-like receptors and NF-κB enhances TF expression during infection (Pawlinski & Mackman, 2010).

Inflammasomes and Thrombo-Inflammation

Inflammasome activation, particularly NLRP3, promotes immunothrombosis by inducing pro-inflammatory cytokines and enhancing TF activity (Fidler et al., 2021). Inflammasome-mediated pyroptosis further amplifies coagulation through the release of intracellular procoagulant factors (Yang et al., 2022).

Complement–Coagulation Crosstalk

The complement system interacts extensively with coagulation pathways, enhancing neutrophil activation, platelet aggregation, and endothelial dysfunction (Markiewski & Lambris, 2007). Complement activation products promote NET formation and thrombin generation, reinforcing immunothrombotic loops (Conway, 2018).

Immunothrombosis in Disease States

Sepsis and Disseminated Intravascular Coagulation

In sepsis, excessive activation of innate immunity leads to uncontrolled immunothrombosis, manifesting as sepsis-induced coagulopathy and disseminated intravascular coagulation (Delabranche et al., 2017; Iba et al., 2019). Microvascular thrombosis impairs tissue perfusion and contributes to multiorgan failure(Levi, 2018).

Viral Infections and COVID-19

Severe viral infections, including COVID-19, exemplify pathological immunothrombosis characterized by endothelial injury, NET overproduction, and platelet hyperreactivity (Ackermann et al., 2020; Middleton et al., 2020). These mechanisms underlie COVID-19-associated coagulopathy and increased thrombotic risk (Bonaventura et al., 2021).

Autoimmune and Chronic Inflammatory Disorders

Chronic inflammatory and autoimmune diseases are associated with persistent immune activation and heightened thrombotic risk mediated by immunothrombosis (Knight et al., 2021). NETs and immune complexes contribute to vascular inflammation and thrombosis in these conditions (Yalavarthi et al., 2015).

Therapeutic Implications and Future Directions

Targeting immunothrombosis requires strategies that balance thrombosis prevention with preservation of host defense (Connors & Levy, 2020). Emerging therapies focus on modulating NET formation, complement activation, and tissue factor signaling rather than indiscriminate anticoagulation (Barnes et al., 2020; Skendros et al., 2020).

Selective inhibition of immune-driven coagulation pathways holds promise for reducing thrombo-inflammatory complications while minimizing bleeding risk (Flick et al., 2014). Future research should prioritize biomarkers distinguishing physiological from pathological immunothrombosis to guide personalized therapy (Rauch et al., 2019).

CONCLUSION

Immunothrombosis represents a fundamental biological bridge between innate immunity and hemostasis. While essential for host defense, its dysregulation drives thrombo-inflammatory disease. A deeper understanding of cellular and molecular mechanisms underlying immunothrombosis will facilitate the development of targeted therapies that mitigate pathological thrombosis without compromising immune protection.

Conflict of Interest

The authors declare no conflict of interest.

Funding

This study received no external funding.

REFERENCES

Engelmann, B., & Massberg, S. (2013). Thrombosis as an intravascular effector of innate immunity. Nature Reviews Immunology, 13(1), 34–45. https://doi.org/10.1038/nri3345

Levi, M., & van der Poll, T. (2017). Coagulation and sepsis. New England Journal of Medicine, 377(12), 1177–1187. https://doi.org/10.1056/NEJMra1607438

Gaertner, F., & Massberg, S. (2016). Blood coagulation in immunothrombosis—At the frontline of intravascular immunity. Thrombosis and Haemostasis, 116(6), 1048–1057. https://doi.org/10.1160/TH16-06-0460

Iba, T., & Levy, J. H. (2020). Sepsis-induced coagulopathy and immunothrombosis. Journal of Thrombosis and Haemostasis, 18(10), 2421–2434. https://doi.org/10.1111/jth.15054

Nicolai, L., & Massberg, S. (2020). Platelets as key players in inflammation and infection. Journal of Thrombosis and Haemostasis, 18(8), 1897–1904. https://doi.org/10.1111/jth.14890

Delabranche, X., Helms, J., & Meziani, F. (2017). Immunothrombosis: A new target for sepsis therapy. Annals of Intensive Care, 7(1), Article 1. https://doi.org/10.1186/s13613-016-0221-8

Aklilu, A., Lai, M. S.-L., Jiang, Z., et al. (2025). Immunothrombosis in sepsis: Cellular crosstalk, molecular triggers, and therapeutic opportunities. International Journal of Molecular Sciences, 26(13), 6114. https://doi.org/10.3390/ijms26136114

Loof, T. G., Mörgelin, M., Johansson, L., et al. (2018). Coagulation, an ancestral serine protease cascade, exerts antibacterial effects. Blood, 131(18), 1936–1947. https://doi.org/10.1182/blood-2017-10-810200

Doolittle, R. F. (2012). Evolution of vertebrate blood coagulation. Cold Spring Harbor Perspectives in Biology, 4(2), a008278. https://doi.org/10.1101/cshperspect.a008278

Esmon, C. T. (2012). Molecular circuits in thrombosis and inflammation. Nature Medicine, 18(6), 846–854. https://doi.org/10.1038/nm.2795

Brinkmann, V., Reichard, U., Goosmann, C., et al. (2004). Neutrophil extracellular traps kill bacteria. Science, 303(5663), 1532–1535. https://doi.org/10.1126/science.1092385

Fuchs, T. A., Brill, A., & Wagner, D. D. (2010). Neutrophil extracellular trap impact on deep vein thrombosis. Proceedings of the National Academy of Sciences of the United States of America, 107(36), 15880–15885. https://doi.org/10.1073/pnas.1005743107

Martinod, K., & Wagner, D. D. (2014). Thrombosis: Tangled up in NETs. Arteriosclerosis, Thrombosis, and Vascular Biology, 34(8), 1741–1749. https://doi.org/10.1161/ATVBAHA.114.303395

Thålin, C., Hisada, Y., Lundström, S., et al. (2019). Neutrophil extracellular traps: Villains and targets in arterial, venous, and cancer-associated thrombosis. Blood, 134(5), 381–390. https://doi.org/10.1182/blood.2019000510

Semple, J. W., Italiano, J. E., Jr., & Freedman, J. (2011). Platelets and the immune continuum. Nature Reviews Immunology, 11(4), 264–274. https://doi.org/10.1038/nri2956

Koupenova, M., Clancy, L., Corkrey, H. A., & Freedman, J. E. (2018). Circulating platelets as mediators of immunity, inflammation, and thrombosis. Circulation Research, 122(2), 337–351. https://doi.org/10.1161/CIRCRESAHA.117.310795

Clark, S. R., Ma, A. C., Tavener, S. A., et al. (2007). Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood. Nature Medicine, 13(4), 463–469. https://doi.org/10.1038/nm1565

Zarbock, A., Singbartl, K., & Ley, K. (2006). Complete reversal of acid-induced acute lung injury by blocking of platelet–neutrophil aggregation. Blood, 107(11), 4481–4489. https://doi.org/10.1182/blood-2005-09-3776

Østerud, B. (2012). Tissue factor expression in blood cells. Thrombosis Research, 129(Suppl 1), S10–S14. https://doi.org/10.1016/S0049-3848(12)70004-3

Pober, J. S., & Sessa, W. C. (2007). Evolving functions of endothelial cells in inflammation. Nature Reviews Immunology, 7(10), 803–815. https://doi.org/10.1038/nri2171

Mackman, N. (2009). Triggers, targets and treatments for thrombosis. Thrombosis and Haemostasis, 102(5), 858–865.

Pawlinski, R., & Mackman, N. (2010). Cellular sources of tissue factor in endotoxemia and sepsis. Thrombosis Research, 125(Suppl 1), S70–S73. https://doi.org/10.1016/S0049-3848(10)70018-3

Fidler, T. P., Xue, C., Yalcinkaya, M., et al. (2021). The AIM2 inflammasome exacerbates atherosclerosis in clonal hematopoiesis. Arteriosclerosis, Thrombosis, and Vascular Biology, 41(8), 2447–2459. https://doi.org/10.1161/ATVBAHA.120.315721

Yang, X., Cheng, X., Tang, Y., et al. (2022). Bacterial endotoxin activates the coagulation cascade through inflammasome-dependent tissue factor release. Nature Immunology, 23(2), 220–232. https://doi.org/10.1038/s41590-021-01093-4

Markiewski, M. M., & Lambris, J. D. (2007). The role of complement in inflammatory diseases from behind the scenes into the spotlight. Nature Reviews Immunology, 7(7), 528–538. https://doi.org/10.1038/nri2137

Conway, E. M. (2018). Reincarnation of ancient links between coagulation and complement. Nature Reviews Immunology, 18(1), 62–72. https://doi.org/10.1038/nri.2017.113

Iba, T., Levy, J. H., Raj, A., & Warkentin, T. E. (2019). Advance in the management of sepsis-induced coagulopathy and disseminated intravascular coagulation. Thrombosis Research, 178, 92–100. https://doi.org/10.1016/j.thromres.2019.04.010

Levi, M. (2018). Pathogenesis and diagnosis of disseminated intravascular coagulation. Critical Care, 22(1), 32. https://doi.org/10.1186/s13054-018-1959-5

Ackermann, M., Verleden, S. E., Kuehnel, M., et al. (2020). Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. New England Journal of Medicine, 383(2), 120–128. https://doi.org/10.1056/NEJMoa2015432

Middleton, E. A., He, X. Y., Denorme, F., et al. (2020). Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. Blood, 136(10), 1169–1179. https://doi.org/10.1182/blood.2020007008

Bonaventura, A., Vecchié, A., Dagna, L., et al. (2021). Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. European Heart Journal, 42(32), 3100–3111. https://doi.org/10.1093/eurheartj/ehab271

Knight, J. S., Caricchio, R., Casanova, J.-L., et al. (2021). The intersection of COVID-19, autoimmunity, and immunothrombosis. Nature Reviews Rheumatology, 17(9), 560–575. https://doi.org/10.1038/s41584-021-00653-3

Yalavarthi, S., Gould, T. J., Rao, A. N., et al. (2015). Release of neutrophil extracellular traps by neutrophils stimulated with antiphospholipid antibodies. Arthritis & Rheumatology, 67(11), 2990–3003. https://doi.org/10.1002/art.39247

Connors, J. M., & Levy, J. H. (2020). COVID-19 and its implications for thrombosis and anticoagulation. Blood, 135(23), 2033–2040. https://doi.org/10.1182/blood.2020006000

Barnes, B. J., Adrover, J. M., Baxter-Stoltzfus, A., et al. (2020). Targeting potential drivers of COVID-19: Neutrophil extracellular traps. Journal of Experimental Medicine, 217(6), e20200652. https://doi.org/10.1084/jem.20200652

Skendros, P., Mitsios, A., Chrysanthopoulou, A., et al. (2020). Complement and tissue factor–enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. Journal of Clinical Investigation, 130(11), 6151–6157. https://doi.org/10.1172/JCI141374

Flick, M. J., Chauhan, A. K., Frederick, M., et al. (2014). The development of inflammatory thrombi requires fibrinogen binding to integrin αIIbβ3. Blood, 123(23), 3636–3644. https://doi.org/10.1182/blood-2013-12-545228

Rauch, P. J., et al. (2019). Loss of hematopoietic stem cell quiescence promotes pathological thrombosis. Circulation, 139(19), 2381–2395. https://doi.org/10.1161/CIRCULATIONAHA.118.037764