

PERSPECTIVE ARTICLE

Immune memory in vascular disease: A trained immunity perspective on in-stent neoatherosclerosis

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Abstract

In-stent neoatherosclerosis (ISNA) has emerged as a major cause of late stent failure, yet its underlying mechanisms remain poorly understood. Clinical and imaging studies indicate that ISNA develops more rapidly and exhibits greater plaque vulnerability than native atherosclerosis, a phenomenon often described as “late catch-up.” Trained immunity (TRIM), a form of innate immune memory driven by metabolic and epigenetic reprogramming, has been increasingly implicated in atherosclerotic cardiovascular diseases but has not previously been linked to ISNA. In this article, we propose a novel hypothesis that ISNA is driven by TRIM in vascular resident cells and innate immune cells within the stented arterial microenvironment. Pre-existing atherosclerotic risk factors may establish central and peripheral TRIM, which can be reactivated by persistent proatherogenic conditions and stent-related stimuli. The rapid recall and amplified secondary responses characteristic of TRIM provide a plausible explanation for the accelerated progression and instability of ISNA lesions. This perspective highlights TRIM as a promising mechanistic framework and therapeutic target for the prevention and management of ISNA.

Keywords: In-stent neoatherosclerosis; Trained immunity; Innate immune memory; Atherosclerotic disease; Stent-related vascular injury; Immunometabolic reprogramming

1. Introduction

Atherosclerosis is a common chronic vascular inflammatory disorder, characterized by the formation of plaques within the arterial intima that contain diverse cell types, lipids, and tissue debris. In coronary artery disease, abdominal aortic aneurysm,

and peripheral arterial disease (PAD), atherosclerosis represents the predominant pathological feature and a major risk factor.¹ The Global Burden of Disease Study 2021 reported that disability-adjusted life years related to atherosclerotic cardiovascular diseases show an increasing trend, particularly in regions with a low sociodemographic index.² The annual percentage change in the prevalence of aortic aneurysm was -0.99% , but both the number of deaths and disability-adjusted life years continued to rise.³ Although the overall global burden of PAD has decreased, it continues to increase in low-sociodemographic-index regions, highlighting significant health inequalities.⁴

At present, stent implantation is widely implemented as a standard therapeutic strategy in clinical practice,

effectively improving perfusion, limb ischemia, and quality of life through revascularization. Compared with simple angioplasty, stent implantation demonstrates a significantly higher procedural success rate (odds ratio: 3.00; 95% confidence interval: 1.14–7.93) and a lower incidence of postoperative complications.^{5,6} Drug-eluting stents (DES) suppress excessive intimal hyperplasia through the local release of antiproliferative agents, largely overcoming the main limitation of bare-metal stents (BMS)—namely, the high incidence of in-stent restenosis (ISR) driven by vascular smooth muscle cell proliferation. Nevertheless, late in-stent thrombosis (IST) has emerged as a new clinical challenge for DES. ISR and IST remain important complications, particularly in patients with coronary artery disease and PAD (Figure 1A).

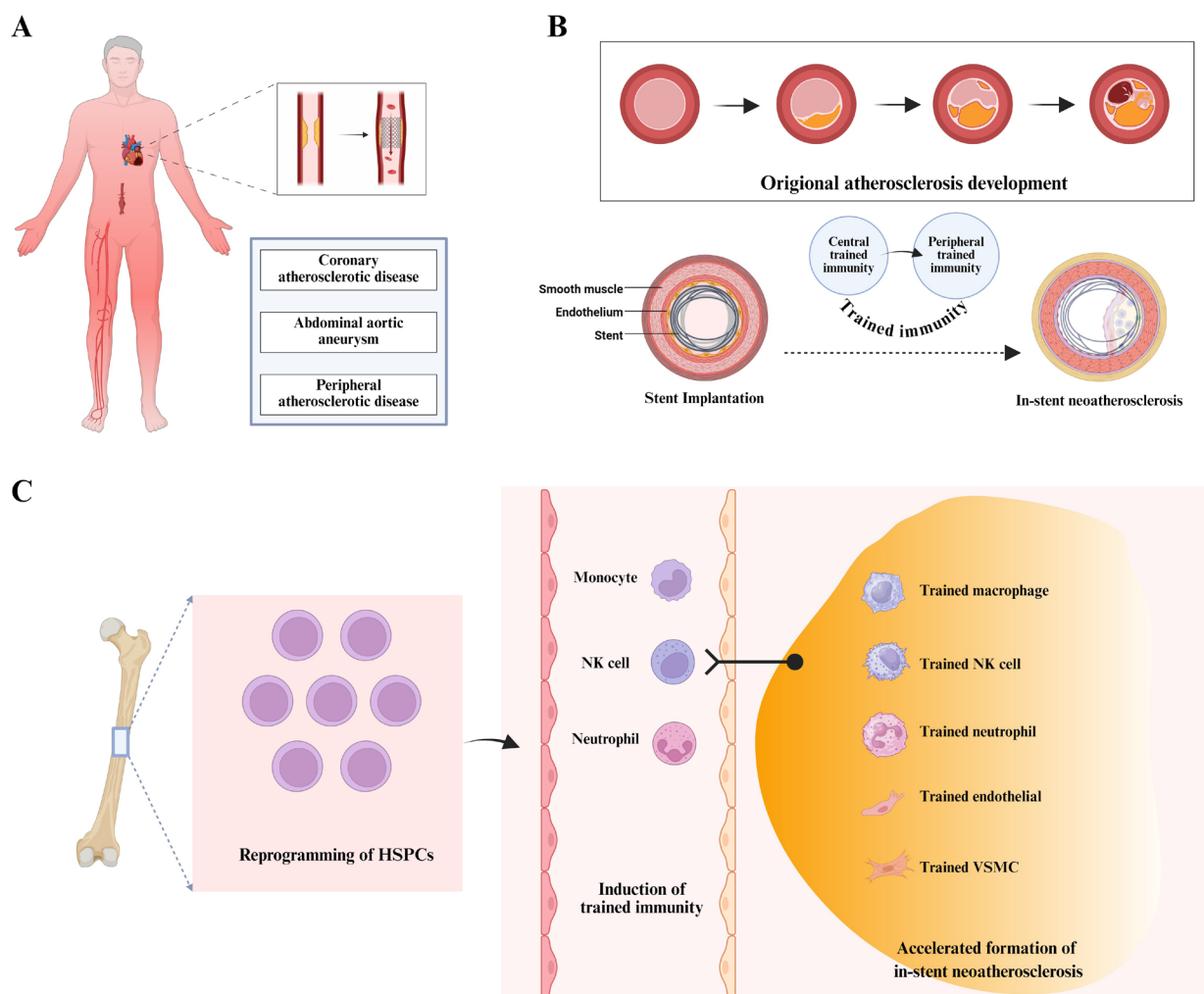


Figure 1. In-stent neoatherosclerosis (ISNA) and trained immunity (TRIM). (A) Common anatomical sites of atherosclerosis in the human body. (B) Key differences between ISNA and native atherosclerosis. (C) Mechanistic insights into the role of TRIM in ISNA development. Created with BioRender. Heng, W. (2026) <https://BioRender.com/p45u023>.

Abbreviations: HSPC: Hematopoietic stem and progenitor cell; NK: Natural killer; VSMC: Vascular smooth muscle cell.

Accumulating evidence indicates that late stent failure is predominantly driven by in-stent neoatherosclerosis (ISNA), which has been recognized as a key pathological basis underlying adverse stent-related events.^{7,8} Notably, compared with native atherosclerosis, ISNA exhibits distinct pathological characteristics, including rapid progression and increased plaque vulnerability.^{9,10} Patients who developed ISNA were significantly older than those who did not (71.3 ± 8.4 vs. 69.0 ± 10.1 years; $p = 0.035$) and had a notably lower estimated glomerular filtration rate ($56.6 [25.0-70.4]$ mL/min/1.73 m² vs. $61.0 [46.3-73.9]$ mL/min/1.73 m²; $p = 0.016$). However, no significant association was observed with sex ($p = 0.914$).¹¹

Additionally, the restenosis rate of the current-generation stents remains as high as approximately 37% one year after implantation.⁷ The neointimal plaques observed within stents are characterized by the presence of lipid-laden macrophages, necrotic cores, calcification, and thin fibrous caps, and exhibit a rapid progression rate.¹² To date, the mechanisms underlying the development of ISNA remain incompletely understood, and there are no therapies that specifically target neoatherosclerosis.

The concept of trained immunity (TRIM) was first proposed in 2011 and refers to the capacity of innate immune cells to develop a rapid and amplified immune response upon secondary stimulation following an initial challenge.¹³ TRIM was initially described in the context of acute infections and vaccination, representing a persistently heightened functional state of innate immune cells, often described as hyperresponsiveness. Accumulating evidence over the past decade has demonstrated its important role in cancer and chronic inflammatory disorders such as rheumatoid arthritis and cardiovascular disease, including atherosclerosis.^{14,15} Both immune and non-immune cells participating in atherogenesis exhibit characteristics of TRIM. Monocytes are heterogeneous and can secrete pro-inflammatory factors, displaying similar metabolic and epigenetic changes to TRIM.¹⁵ TRIM also resides in bone marrow progenitor cells, where epigenetic and metabolic reprogramming activate the NOD-, LRR-, and pyrin domain-containing protein 3 inflammasome and interleukin-1 signaling pathway, leading to persistent immune hyperreactivity.¹⁶ Furthermore, non-immune cells, such as endothelial cells, can establish long-lasting immune memory under the activation of oxidized low-density lipoprotein and hyperglycemia, thereby enhancing immune function.^{17,18}

In summary, TRIM contributes to the pathophysiological process of atherosclerosis by mediating adverse inflammatory responses. However, no studies to date have reported the involvement of TRIM in the initiation

or progression of ISNA. On this basis, we propose for the first time that the formation of ISNA is driven by TRIM in vascular resident cells and innate immune cells (Figure 1B). This process essentially represents an immune memory-like behavior within the vascular microenvironment.

2. Trained immunity promotes the progression of atherosclerotic cardiovascular diseases

Trained immunity is defined as a long-lasting and recallable innate immune phenotype that can be reactivated upon subsequent stimulation and is primarily regulated by immunological signaling, metabolic reprogramming, and epigenetic modifications.¹⁹⁻²¹ TRIM plays a crucial role in host defense against infection and is thus regarded as an evolutionarily selected adaptive immune response. It enhances the host's defensive capacity against subsequent injurious challenges, such as pathogenic infections, thereby significantly improving host survival. Moreover, studies have demonstrated that TRIM also exerts protective effects against tumors.²²⁻²⁶

However, it is important to note that TRIM may also trigger excessive inflammatory responses, contributing to or exacerbating the development of chronic inflammatory diseases. Based on anatomical origin, TRIM can be broadly classified into central TRIM, which mainly arises from bone marrow hematopoietic stem and progenitor cells (HSPCs), and peripheral TRIM, which primarily involves circulating and tissue-resident innate immune cells. Notably, peripheral TRIM is not restricted to monocytes/macrophages, natural killer cells, or neutrophils; it can also be induced in non-immune cells, including endothelial cells and vascular smooth muscle cells.

Studies have shown that exposure of innate immune cells to damage-associated molecular patterns or pathogen-associated molecular patterns, followed by their engagement with pattern recognition receptors, activates intracellular signaling pathways and promotes the translocation of specific transcription factors (e.g., nuclear factor κ -light-chain-enhancer of activated B cells, nuclear factor for interleukin-6 expression, activator protein-1, interferon regulatory factors, and signal transducer and activator of transcription) into the nucleus, thereby initiating the transcription of host defense genes. Concurrently, this process induces metabolic reprogramming and long-term epigenetic alterations, thereby establishing TRIM. A variety of ligands capable of inducing TRIM have been identified, including microorganisms, oxidized lipoproteins, hyperglycemia, and catecholamines.¹⁵ Upon exposure to exogenous or endogenous stimuli, innate immune cells undergo intracellular metabolic reprogramming,

encompassing enhanced glycolysis, glutaminolysis, and mevalonate synthesis. These metabolic changes ultimately lead to epigenetic modifications, such as alterations in histone modifications, DNA methylation, and long non-coding RNA expression. Together, these processes induce sustained epigenetic reprogramming that underlies the trained immune phenotype.^{14,27}

Atherosclerotic vascular disease is a complex, multifactorial chronic disorder—the initiation and progression of which are influenced by genetic susceptibility, lifestyle factors, and comorbid conditions (Figure 1C). Increasing evidence indicates that traditional atherosclerotic risk factors, unhealthy lifestyle behaviors,

and inflammatory comorbidities can all induce TRIM (Table 1). This process activates inflammatory memory in innate immune cells and thereby accelerates the progression of atherosclerosis.^{14,28,29} Dyslipidemia is one of the most significant risk factors for atherosclerotic vascular disease. Studies have shown that *in vitro* pre-treatment of isolated human primary monocytes with low concentrations of oxidized low-density lipoprotein for 24 hours, followed by differentiation into macrophages in a neutral medium for five days, can induce TRIM. These differentiated macrophages exhibit increased secretion of cytokines, chemokines, and matrix metalloproteinases, along with enhanced foam cell formation upon subsequent stimulation.³⁰

Table 1. Atherosclerosis-associated risk factors

Risk factors		Trained cells	Molecular mechanisms	Targets	Reference
Traditional risk factors		Monocytes	Oxidized phospholipids	-	31
	Hyperlipidemia	Vascular smooth muscle cells	Histone H3 lysine 9 dimethylation	G9A/GLP (G9A-like protein)	32
	Hypertension	Monocytes	↑ fatty acid synthesis	-	33
	Hyperglycemia	Macrophages	↑ glycolysis	Runx1	34
		Endothelial cells	SET domain-containing protein 7	-	35
Lifestyle-related factors	Psychosocial stress	Hematopoietic stem and progenitor cells	↑ glycolysis	-	36
	Western diet	Myeloid progenitor cells	NLRP3 inflammasome	-	37
	Physical inactivity	Hematopoietic stem and progenitor cells	↓ leukocyte	-	38
Inflammatory diseases	Infection	Monocytes/macrophages	Histone methylation and acetylation; glycolysis	-	39
	Periodontitis	Hematopoietic stem and progenitor cells	↑ neutrophils	-	40
	Gout	Monocytes	AKT-PRAS40 autophagy pathway	-	41
	Rheumatoid arthritis	CD14 ⁺ monocytes	STAT3	STAT3	42
Others	End-stage renal disease	Monocytes	AhR-dependent arachidonic acid pathway	-	43

Note: ↑ indicates increased or enhanced, whereas ↓ indicates decreased or inhibited.

Abbreviations: AhR: Aryl hydrocarbon receptor; AKT-PRAS40: Protein kinase B–proline-rich protein kinase B substrate of 40 kDa; CD: Cluster of differentiation; G9A: Euchromatic histone lysine methyltransferase 2; GLP: Glucagon-like peptide-1; NLRP3: NOD-, LRR-, and pyrin domain-containing protein 3; STAT3: Signal transducer and activator of transcription 3.

Edgar *et al.*³⁴ demonstrated that bone marrow-derived macrophages from diabetic mice acquire pro-inflammatory gene expression and proatherogenic functional features through a glycolysis-dependent mechanism. Importantly, these characteristics are retained even under physiological glucose conditions, indicating the establishment of TRIM. When bone marrow from diabetic mice was transplanted into normoglycemic *Ldlr*^{−/−}

mice, atherosclerotic progression was markedly enhanced. These findings provide a mechanistic explanation for why glucose-lowering therapies alone fail to effectively reduce the risk of macrovascular complications in patients with diabetes.

In another study, monocytes and macrophages from mice subjected to myocardial infarction and ischemia–reperfusion injury maintained a TRIM phenotype with

proatherogenic properties, thereby accelerating the progression of atherosclerosis. This observation offers insight into why survivors of acute coronary syndromes continue to face a high risk of recurrent atherosclerosis-related vascular events.⁴⁴ Several comprehensive reviews have summarized the mechanisms and implications of TRIM in atherosclerotic vascular disease.^{14,15,28}

3. The “late catch-up” phenomenon in in-stent neoatherosclerosis

In-stent neoatherosclerosis has emerged as a major cause of stent implantation failure.⁷⁻⁹ A report from the PRESTIGE Consortium,^{45,46} which analyzed optical coherence tomography findings in 134 patients with very late stent thrombosis, reported that 58 patients exhibited concomitant ISNA. In addition, DES implantation was significantly associated with the development of ISNA. Notably, increased macrophage infiltration was indicative of heightened plaque vulnerability, which may lead to advanced atherosclerotic plaque rupture.

Although clinical studies investigating ISR and IST are heterogeneous, several conclusions can be drawn with reasonable certainty. First, the stent type does not appear to alter long-term adverse outcomes. Stent implantation provides permanent vascular support, reducing immediate vascular retraction and stabilizing blood flow. Currently, the commonly used stents in clinical practice mainly include DES and BMS. DES are coated with agents that inhibit intimal hyperplasia, significantly reducing the incidence of ISR within the stent, although they cannot completely prevent it.⁴⁷ BMS lack a drug coating and are associated with a relatively higher risk of postoperative restenosis. Both DES and BMS develop comparable rates of ISNA during long-term follow-up, with ISNA occurring earlier and more frequently in DES.⁸

Second, the timing of ISNA formation is variable but generally occurs within months to a few years after stent implantation. This time course is substantially shorter than that of native atherosclerosis, which typically evolves over decades.⁴⁸ Third, the incidence of ISNA increases progressively with longer duration after stent implantation.⁴⁹

Accordingly, two intriguing forms of the “late catch-up” phenomenon have been recognized.¹⁰ First, although DES substantially mitigate the limitations of BMS, both DES and BMS exhibit sustained neointimal hyperplasia in long-term follow-ups of 5–10 years, with no significant difference in the rates of ISR and IST between the two. Second, compared with native atherosclerosis, ISNA develops over a markedly shorter time frame and is associated with poorer plaque stability. These observations suggest that the

host exhibits heightened sensitivity to the atherosclerotic microenvironment and to stent-related stimuli. Moreover, vascular resident cells and innate immune cells appear to have acquired a persistent form of immune memory.

4. Trained immunity opens the door to in-stent neoatherosclerosis

On this basis, we propose that TRIM represents a principal mechanism driving the development of ISNA, with several potential implications. First, pre-existing atherosclerotic risk factors can induce the establishment of TRIM (Table 1). Even if highly inflammatory innate immune cells in the circulation and peripheral tissues are turned over through metabolic clearance, central TRIM derived from bone marrow HSPCs can maintain sustained responsiveness to subsequent stimuli.

Second, although local vascular pathological injury is alleviated after stent implantation, the systemic atherosclerotic microenvironment, such as hyperlipidemia, hyperglycemia, systemic inflammation, and other proatherogenic factors—including the accumulation of lipid-laden foam macrophages, endothelial dysfunction, immune cell infiltration, and aberrant secretion of pro-inflammatory cytokines and chemokines—persist.^{50,51} These conditions provide a permissive milieu for the reactivation and amplification of TRIM-associated cellular responses.

In addition, stent-related stimuli may further exacerbate local vascular effects. Following stent deployment, the vascular wall undergoes substantial dilation, triggering an inflammatory response and resulting in plaque compression. Over time, this plaque may evolve into a source of growth factors, chemokines, and cytokines, thereby promoting the development of ISNA. Finally, the defining features of TRIM—namely rapid recall responses and amplified secondary activation—offer a compelling explanation for the accelerated progression and poor stability of ISNA lesions.

Previous investigations into the injurious mechanisms underlying ISNA have been substantially constrained by methodological and technical limitations.⁵²⁻⁵⁵ The integration of multi-omics approaches, including single-cell sequencing, spatial omics, metabolomics, and radiomics, may enable a more in-depth dissection of the molecular basis of ISNA. One single-cell sequencing study has delineated TRIM-like responses in human monocytes under diverse stimuli.⁵⁶ Importantly, a recent study successfully developed the first mouse model that recapitulates the distinctive features of human ISNA, providing a valuable platform for mechanistic studies and the development of therapeutic strategies.^{12,57}

5. Targeting trained immunity for the treatment of in-stent neoatherosclerosis

At present, effective strategies for the prevention and treatment of ISNA remain limited.⁷ With the establishment of the TRIM framework, TRIM has emerged as a potential breakthrough target for ISNA intervention. Since TRIM plays a critical role in host defense, its chronic suppression may increase susceptibility to infections and the development and progression of malignancies. Furthermore, the metabolic and epigenetic mechanisms that drive TRIM are also essential for many other cellular functions. Therefore, it is crucial to develop strategies that enhance specificity and selectively disrupt only maladaptive trained immune responses.

Nanobiologic agents are lipid nanoparticles composed of natural molecules, which offer advantages such as structural stability, specific targeting of myeloid cells, and biocompatibility, while also being capable of loading small-molecule drugs to modulate TRIM. Consequently, nanotherapeutic approaches show considerable preclinical potential for the targeted recognition and modulation of TRIM.⁵⁸⁻⁶¹ We have previously developed anti-Ly6G antibody-conjugated nanoparticles that selectively target neutrophils, enabling the diagnosis and monitoring of abdominal aortic aneurysm.⁶¹ However, the development of imaging tracers remains constrained, and distinguishing TRIM from other immune processes continues to be challenging.⁶²

In addition, further clarification of the molecular targets underlying TRIM will facilitate the development of integrated diagnostic and therapeutic platforms specifically tailored to ISNA. Duivenvoorden *et al.*⁶³ constructed recombinant high-density lipoprotein nanoparticles capable of delivering statins selectively to atherosclerotic lesions, thereby directly attenuating intraplaque inflammation in murine models of atherosclerosis. In another study, van Leent *et al.*⁶⁴ developed a rapamycin-loaded nanobiologic that efficiently delivered the drug to bone marrow progenitor cells, highlighting the feasibility of targeting central TRIM at its source. At the same time, against the backdrop of rapidly evolving digital lifestyles, clarifying the specific molecular processes of TRIM within ISNA will drive the innovation of new bio-sensing technologies. For instance, sensors constructed from advanced materials such as poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) are expected to achieve high-sensitivity dynamic monitoring of disease markers, thereby providing a new possibility for the early warning of cardiovascular diseases.^{65,66}

The periosteum is heavily innervated by the sympathetic

nervous system, which regulates the HSPC niche. Studies have shown that the reprogramming of HSPCs is regulated by the sympathetic nervous system in the bone marrow and associated catecholamine signaling pathways, both of which have been demonstrated to induce TRIM.¹⁵ Consequently, pharmacological interventions targeting the nervous system to specifically modulate myeloid cells may offer a potential strategy for attenuating TRIM. Moreover, therapeutic strategies based on inflammatory reprogramming and immune modulation, including monoclonal antibodies, small interfering RNA, mRNA-based approaches, epigenetic reprogramming, and gene-editing technologies, hold substantial potential for reversing or mitigating ISNA.⁶⁷

6. Conclusion

In summary, the mechanisms underlying the development of ISNA remain poorly understood, and the emergence of the TRIM paradigm provides an important conceptual opportunity. On the one hand, integrating multi-dimensional technologies such as single-cell omics, spatial omics, and metabolomics can elucidate the regulatory mechanisms of TRIM in ISNA, for example, by revealing the spatiotemporal dynamic changes of key immune cells like monocytes or macrophages. On the other hand, based on these mechanisms, novel diagnostic and therapeutic strategies for ISNA should be explored, incorporating new biosensing technologies to achieve early and precise detection. Furthermore, well-structured clinical cohort studies can be conducted to progressively evaluate the safety and efficacy of targeted ISNA interventions and to promote their transformation into clinical practice. Collectively, we propose for the first time that TRIM represents a central mechanism contributing to the progression of ISNA.

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Conflict of interest

The authors declare they have no competing interests.

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Not applicable.

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Further disclosure

During the preparation of this manuscript, ChatGPT was utilized to enhance language and readability. After using this tool, the authors reviewed and edited the content as necessary and take full responsibility for all content of the publication.

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