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Review Article

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A review of the current state in neointimal hyperplasia development following endovascular intervention and minor emphasis on new horizons in immunotherapy

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ABSTRACT

Endovascular strategies play a vital role in the treatment of peripheral arterial disease (PAD). However, luminal loss or restenosis after endovascular intervention remains a significant challenge. The main underlying mechanisms are negative vascular remodeling and elastic recoil in balloon angioplasty. During stenting, the main reason for this complex is neointimal proliferation. Endothelial cell injury due to endovascular intervention initiates a series of molecular events, such as overexpression of growth factors, cytokine secretion, and adhesion molecules. These induce platelet activation and inflammatory processes, which trigger the proliferation and migration of vascular smooth muscle cells into the intima, resulting in neointimal hyperplasia. During this process, PAD progression is mainly caused by chronic inflammation, in which macrophages play a central role. Of the current strategies, drug release interventions aim to suppress restenosis using antiproliferative drugs, such as sirolimus and paclitaxel, during drug release. These drugs inhibit vascular reendothelialization and reduce late in-stent restenosis. For this reason, immunotherapy can be considered an important alternative. Interventions that polarize macrophages to the M2 subtype are particularly important, as they shape the immune response in an anti-inflammatory direction and contribute to tissue repair. However, there are several challenges to overcome, such as localizing antiproliferative or polarizing agents only to areas of vascular injury. This review discusses, based on the early study observations, immunotherapeutic approaches to prevent restenosis after endovascular intervention for the treatment of PAD.

Keywords: Peripheral Arterial Disease; Stent; Stenosis; Immunotherapy; Macrophage; Phenotype

INTRODUCTION

Peripheral arterial disease (PAD) is a significant burden on healthcare systems, affecting more than 200 million people worldwide [1,2]. Clinically, it ranges from asymptomatic to severe life-threatening presentations [3]. If PAD patients are left untreated, cardiac events, such as myocardial infarction and events related to the central nervous system, such as stroke, are likely to develop [4].

Endovascular strategies have been the first-line therapy for symptomatic PAD, although there is no consensus on which method should be prioritized [4]. Unfortunately, luminal loss and restenosis after endovascular interventions has been a significant challenge [5]. The underlying mechanisms are complex; however, this phenomenon is mainly due to negative vascular remodeling and elastic recoil in the case of balloon angioplasty (BA) or neointimal proliferation in the case of stenting [6,7].

The occurrence of restenosis in the pre-stent period ranged 40–60% in percutaneous transluminal angioplasty [6]. It decreased to 17–41% during the period of bare metal stent, predominantly mitigating the effects of elastic recoil and negative remodeling. The formation of neointimal proliferation leading to in-stent restenosis (ISR) is a result of the response to injuries occurring after endovascular intervention. Although there is ISR due to neointimal proliferation after BA, this mechanism occurs more exaggeratedly in stent cases [6,8,9]. Drug-eluting stents (DES) have further reduced the rate of restenosis to < 10%, especially with the introduction of the second generation, a biodegradable and biocompatible polymer that provides controlled drug release, and a drug-coated balloon [10,11]. Although early elastic recoil and vascular remodeling were prevented to some extent by the stents, restenosis associated with neointimal hyperplasia could not be completely prevented in the long term [9]. The underlying mechanisms may induce factors associated with functional impairment of PAD, and a better understanding of these pathways may help guide new medical therapies for treatment [12]. Immunotherapeutic approaches are also being investigated for this reason [13,14].

This review aims to evaluate the role of immunotherapy in the prevention of restenosis after endovascular intervention in the treatment of PAD.

VASCULAR RESPONSE TO ENDOVASCULAR INTERVENTION

Despite promising technological advances in stent technology, managing the balance between revascularization of the target lesion and restenosis after endovascular intervention remains a highly complex issue owing to the underlying molecular mechanisms.

Both BA and stent placement disrupt the endothelial cell (EC) layer. EC damage affects not only the function of the vascular barrier, but also its secretory function [15]. This EC injury initiates a series of molecular events that induce platelet activation and aggregation, followed by infiltration of leukocytes and monocytes into the lesion site [16]. Platelets and inflammatory cells secrete growth factors, such as fibroblast growth factor 2 (FGF-2), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF). These growth factors are responsible for initiating vascular smooth muscle cells (VSMCs) proliferation through tyrosine kinase receptors [16,17]. VSMCs switch from a quiescent contractile phenotype to a synthetic phenotype and migrate to the intima. The shifted VSMC migration into the intima and the accumulation of extracellular matrix are hallmarks of intimal hyperplasia [16]. Circulating mitogens, such as angiotensin II and plasmin, may be involved in VSMC proliferation and migration owing to overexposure based on endothelial denudation [18] (**Fig. 1**).

Importantly, matrix metalloproteinases (MMPs) are known to play a key role in the degradation of proteins such as collagen and elastin. In particular, MMP-2 and -9 appear to be clearly involved in the migration of SMCs to the intima and promote the development of

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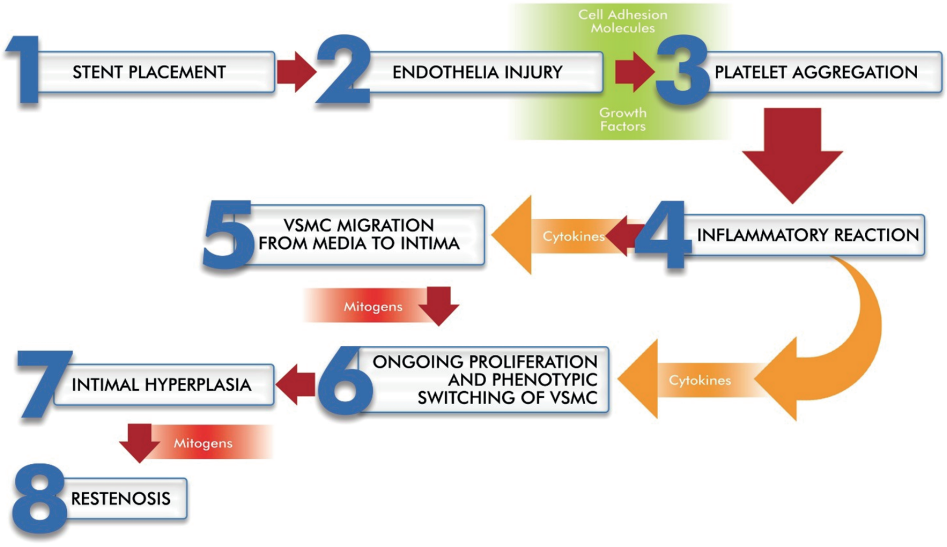

Figure 1. Basic steps of restenosis after stenting.

intimal hyperplasia in *in vivo* models. Inhibition of MMP activity is envisioned as an approach in the treatment of cardiovascular diseases [19].

Although specific mechanisms are unclear, various factors, such as oxidized low-density lipoprotein (LDL), hyperglycemia, and reactive oxygen species, cause vascular endothelial damage. This damage, which can be attributed to abnormal signaling of cytokines and other molecules, results in alterations in gene expression and cellular behavior [20,21]. Endothelial progenitor cells (EPCs) play an important role in endothelial repair and angiogenesis by differentiating into mature ECs [16]. Due to this feature of EPC, 3 basic mechanisms are of great importance in the treatment of endothelial damage: transport of EPCs to endothelial injury sites, delivery of certain genes to EPCs, and use of certain drugs that can delay the aging of EPCs. Some drugs, such as LDL-cholesterol-lowering and anti-diabetic drugs, are already used to reduce adverse events in risky patients [22-24].

Remodulation of the imbalance between stimulatory growth factors/cytokines (such as PDGF, FGF, transforming growth factor [TGF]-β, and IGF-1) and inhibitory factors (endothelial-derived nitric oxide) that occurs as a result of injury can be envisioned as important therapeutic targets. In this context, vascular endothelial growth factor (VEGF, particularly VEGF-A), which acts nitric oxide-dependently, is one of the most extensively studied targets in preclinical studies [16,25].

MONOCYTE/MACROPHAGE RESPONSE FOLLOWING ENDOVASCULAR INTERVENTION

Stent implantation also induces immune cell migration by activating the expression of cell adhesion molecules, such as ICAM-1, PECAM-1, and VCAM-1, around the stent strut. Subsequently, monocytes that adhere to these cell adhesion molecules migrate to the subendothelial space and transform into macrophages, M1 or M2 depending on microenvironmental signals [26]. These significant changes in immune populations may explain the clinical phenotypes of restenosis and their variation in severity [5].

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These cells produce pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and interferon-γ. These cytokines contribute to the progression of the inflammatory process and, therefore, to stenosis [27] (**Fig. 1**). On the contrary, anti-inflammatory cytokines, such as IL-10 and TGF-β, also play a role in this process. The balance between pro-inflammatory and anti-inflammatory responses significantly determines the extent of disease progression [28].

Among these immune cells, macrophages play a predominant role in maintaining chronic inflammation [29]. However, macrophages do not exist as pure populations at the sites of vascular inflammation. Diversity and plasticity are the 2 distinguishing features of macrophages. Classically activated M1 macrophages are pro-inflammatory, associated with VSMC switching, and increase endothelial damage by secreting lytic enzymes. Alternatively, activated M2 macrophages are associated with anti-inflammatory reactions and tissue remodeling [14]. M2 macrophages can be further divided into subphenotypes: M2a (wound healing/anti-inflammatory), M2b (immune-mediated/pro-inflammatory), M2c (regulatory/anti-inflammatory), and M2d (tumor-associated/proangiogenic). However, in in vivo studies it is generally discussed as the broad M2 phenotype [30].

Following endovascular injury, monocytes initially adhere to adhesion molecules and differentiate into M1 macrophages, which sustain further endothelial damage and facilitate smooth muscle cell proliferation during restenosis [25]. M2 macrophages triggered by IL-4 and IL-13 contribute to tissue repair by secreting several molecules such as fibronectin and IGF-1. The M2 phenotype also secretes anti-inflammatory cytokines, primarily IL-10 and TGF-β [31]. However, the precise role of each subset is not yet known in the context of PAD [12]. The presence of CD68-positive and CD86-positive M1 macrophages on immunohistochemical examination suggests the presence of phagocytic inflammatory macrophages and inflammation in the neointima. IL-33 secreted by damaged ECs promotes M1 differentiation. IL-37, in contrast, promotes CD206-positive M2 and suppresses the M1 macrophage phenotypic switch [28].

ANTIPROLIFERATIVE EFFECTS OF CURRENT DEB/DES USE

Paclitaxel or sirolimus that is the most commonly used have an antiproliferative effect only during the elution period of the drug [32,33]. Furthermore, these agents are both nonspecific and cytotoxic, and significantly increase the risk of long-term morbidity and mortality due to their off-target effects, which are activity that differs from the targeted biological effect [32,34]. Due to the broader therapeutic index and lower risk of dose-related toxicity, less mortality outcomes are expected for sirolimus [35]. On the other hand, a meta-analysis study comparing paclitaxel-coated devices with control arms showed that the mortality rate gradually increased in patients treated with paclitaxel-coated devices at follow-up up to the 5th year, despite a similar mortality rate at first year [36]. To address these challenges, a new generation of biodegradable stents and cell-selective drugs are currently in development [8,37,38].

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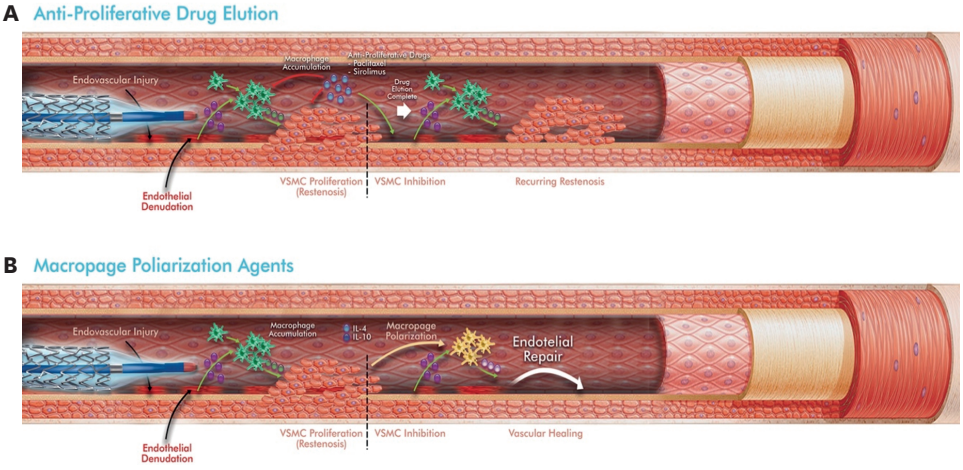

Figure 2. Differences between drug eluting endovascular interventions (A) and macrophage polarization (B) in preventing restenosis. Green cells, M1 (pro-inflammatory) macrophages; Yellow cells, M2 (anti-inflammatory) macrophages. Adapted from [32], with permission from Tan et al.
VSMC, vascular smooth muscle cell.

IMMUNOTHERAPY IN RESTENOSIS

Antiproliferative drugs used to prevent vascular EC proliferation inhibit reendothelialization between the metal surface of the stent and the blood. This reduces long-term vascular healing and increases late ISR and stent thrombosis due to blood contact with the metal surface of the stent [39,40] (**Fig. 2A**).

Immunotherapy can be considered an important alternative in the prevention of ISR because the chronic vascular inflammation is known to play a central role in the progression of restenosis. However, immunotherapies are not currently recommended for the clinical management of PAD. On the other hand, several small-sized studies in human have demonstrated the therapeutic benefits of therapies that reduce inflammation, such as anti-IL-1β and anti-TNF-α agents [41-43]. Although they have promising anti-inflammatory effects, they may cause immune-related off-target effects in perivascular or other distant areas due to the pleiotropic nature of cytokines (affecting multiple systems or more than one phenotype), especially during systemic administration [44].

The most appropriate approach should be to identify the specific pathology in the pathways involved in restenosis and apply individual treatments. For example, rare defects in genes related to nitric oxide signaling have been observed in members of a family with early myocardial infarction. However, causal pathway pathologies remain unclear [45]. Macrophages play a dominant and central role in maintaining chronic inflammation [14]. Moreover, M1 macrophages sustain further endothelial damage, shape the immune response in the inflammatory direction, and facilitate proliferation and phenotypic changes of VSMC by secreting pro-inflammatory cytokines during restenosis development [29]. In addition, M2 macrophages shape the immune response in an anti-inflammatory manner and contribute to tissue repair [31]. In this context, macrophages can be considered an important and effective therapeutic target for preventing and resolving vascular inflammation. This approach for targeting macrophages can be achieved primarily in 2 ways:

1) By reducing the increase in the number of M1 macrophages following endovascular intervention by administration of certain agents, such as inhibitors of typical

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inflammatory cytokines (IL-1β, TNF-α, and IL-6), chemokines (CCL2 and CCL3), or growth factors [13], or

2) By rapidly polarizing them towards M2 phenotype by administering some polarizing molecules such as IL-4, IL-10, TGF-β1, and PGE2 [46].

Several animal studies have shown that therapeutic M2 polarization (**Table 1**) [47-51], which is the second approach, is associated with plaque regression and has a permanent effect on the disease [52]. However, in these applications, even if the local inflammation is reduced, undesirable and uncontrollable systemic events may develop. Adopting this approach intravenously also requires further consideration of the known blood flow effects [32]. Some bioengineered materials, such as polylactic-co-glycolic acid polymer-coated scaffolds, can make a significant contribution by providing controlled and local release of some molecules that provide M2 macrophage polarization (**Fig. 2B**) [48]. However, it is difficult to avoid the systemic effects of these agents owing to degradable polymers or passive absorption. To localize these agents only to the areas of vascular injury, nanoparticles (NPs) decorated with target ligands may be a more reasonable solution [32] (**Fig. 3A**). Indeed, NPs have recently found a wide range of studies for treatment and diagnostic purposes. However, it should not be ignored that some of them tend to show toxicity at the cellular level in tissues and organs. Some NPs can even produce highly reactive forms of oxygen that can cause tissue damage, including inflammation and other toxic effects [53,54]. Modification strategies to increase the safety of NPs should be evaluated in detail, taking into account their physical and pharmacokinetic properties.

Some studies on magnetic nanoparticles (MNPs) coated with target ligands and therapeutic agents have reported that MNPs can be localized around targeted tissues such as malignant tissue by applying an external magnetic field (EMF) [55]. This type of strategy may also be envisaged for preventing luminal loss after endovascular intervention if the implant is made of nonmagnetic alloys. After systemic administration, MNPs loaded with target ligands and M2-polarizing agents can be localized at sites of vascular injury by applying an EMF (**Fig. 3B**).

Table 1. Selected examples investigating macrophage polarization in preclinical peripheral arterial disease

Study	Polarizing application	Essential mechanism	Control	Experimental model	Outcomes	Ref.
Hachim et al. (2017)	IL-4 loaded mesh	M2 polarization	Unloaded mesh	C57BL6 mice	- Decreased M1/M2 ratio - Diminished formation of fibrotic capsule surrounding implant	[47]
Pellegrin et al. (2014)	Ischemic condition	M1 polarization	Non-ischemic conditions	C57BL6 mice	Early stage: - Increased M1/M2 ratio - Increased IFN-γ/IL-4 ratio Later stages: - Neutral state of the polarization	[48]
Ganta and Annex (2021)	Anti-$VEGF_{165}$b monoclonal antibody	VEGFR1 inhibition	Placebo	C57BL6	- Increased S100A8/S100A9 - Increased M1/M2 ratio	[49]
Fu et al. (2018)	Hydrogen-saturated water	M2 polarization	Dehydrogenized water	Balb/c mice	- Decreased M1/M2 ratio - Decreased ROS	[50]
Wolfs et al. (2014)	Helminth-derived soluble egg antigens	M2 polarization	PBS	C57BL6 mice	- Decreased M1/M2 ratio - Increased IL-10 production - Decreased intraplaque TNF-a, MCP-1, ICAM-1, VCAM-1, and CD68	[51]

VEGFR1, downstream regulators of macrophage polarization; S100A8/S100A9, downstream mediator of M1 macrophages.
IL, interleukin; INF, interferon; PBS, phosphate buffered saline; TNF, tumor necrosis factor; MCP-1, monocyte chemotactic protein-1; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

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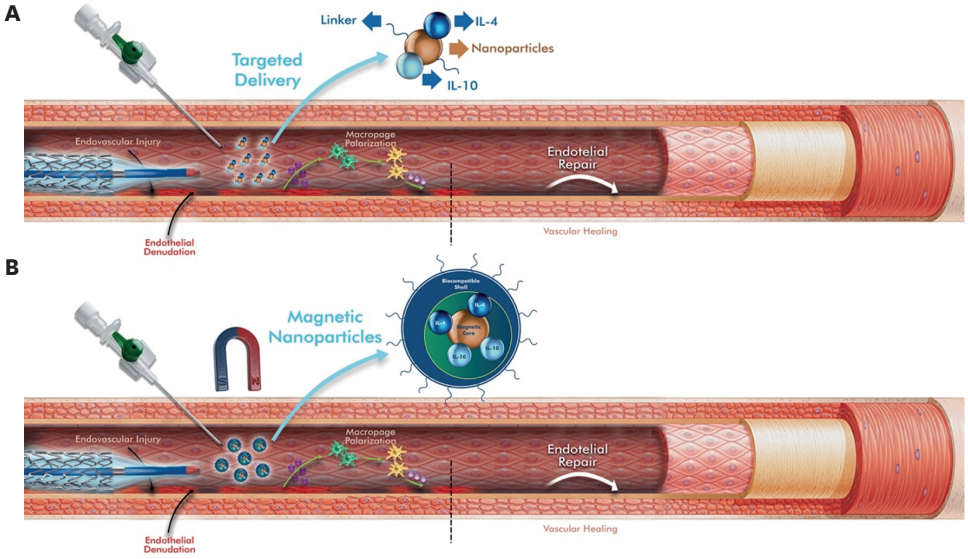

Figure 3. Schematic representation of 2 proposed ways to localize cell polarizing agents at sites of vascular injury. (A) Nanoparticle loaded with targeting ligands and cell-polarizing agents. (B) Shell-coated magnetic nanoparticles loaded with targeting ligands and cell polarizing agents, the localization effect of which is enhanced by the application of an external magnetic field. Adapted from [32], with permission Tan et al.
IL, interleukin.

We can expect an optimal result from this application when performed from the outer surface of the body closest to the site of vascular injury. Because localized immunotherapy enhances the macrophage-polarizing effect and reduces non-specific immune responses, similar to the results of cancer treatments [56].

Various pharmacological treatments that can be applied instead of or in addition to invasive treatment to prevent restenosis have been investigated. These drugs, which can be grouped into several main groups, are used to prevent neointimal growth due to the proliferation of smooth muscle cells according to the pathophysiological mechanism that may cause restenosis (**Table 2**).

Table 2. Selected pharmacological drugs against in stent restenosis (modified from [57], with permission of Patel et al.)

Group	Immunosuppressive	Antiproliferative	Migration inhibitor	Accelerator of healing	Antithrombin
Selected agents	Limus group:	Taxol (paclitaxel)	Batimastat	VEGF	Heparin
	Sirolimus	Actinomycin	Prolylhydrosylase inhibitors	17b-estradiol	Hirudin and iloprost
	Tacrolimus	Methotrexate	C-proteinase inhibitors	EPC antibodies	Abciximab
	Everolimus	Mitomycin	Metalloproteinase inhibitors	TKI	
	Zotarolimus	C-myc antisense			
	Others:	Taxol derivative (QP-2)			
	Methylprednisolone				
	Dexamethasone				
	Cyclosporine				
	Mycophenolic acid				
	Interferon-1b				
	Tranilast				
	Leflunomide				
Main characteristics	Stopping cell cycle	Weakening neointimal growth	Preventing endothelial cell migration into the stent	Promoting healing of the vascular system	Preventing stent thrombosis and platelet aggregation

VEGF, vascular endothelial growth factor; EPC, endothelial progenitor cell; TKI, tyrosine kinase inhibitor.

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CONCLUSION REMARK

Endovascular interventions play a life-saving role in PAD treatment. Significant advances have been made in endovascular intervention over the past 2 decades. However, restenosis after endovascular intervention remains a significant challenge. Despite the new and different platforms that release drugs, the long-term risks of morbidity and mortality remain unresolved. Current early studies show that immunotherapies aimed at modulating macrophages to the M2 subset hold strong promise. Developments that enable immunomodulatory agents to be localized only in the stented area will play a vital role in preventing side effects following PAD treatment.

LIMITATION OF THIS STUDY

This review had some limitations. Currently, there are no immunotherapeutic medications in clinical use for PAD treatment. Therefore, the review was designed in a traditional format, and only the findings of promising early study reports were highlighted. Several issues need to be addressed, such as effectiveness, safety, and standardization.

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