Review

Research Progress on the Pathogenesis and Treatment of Neoatherosclerosis*

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[Abstract] Neoatherosclerosis (NA) within stents has become an important clinical problem after coronary artery stent implantation. In-stent restenosis and in-stent thrombosis are the two major complications following coronary stent placement and seriously affect patient prognosis. As the common pathological basis of these two complications, NA plaques, unlike native atherosclerotic plaques, often grow around residual oxidized lipids and stent struts. The main components are foam cells formed by vascular smooth muscle cells (VSMCs) engulfing oxidized lipids at lipid residue sites. Current research mainly focuses on optical coherence tomography (OCT) and intravascular ultrasound (IVUS), but the specific pathogenesis of NA is still unclear. A thorough understanding of the pathogenesis and pathological features of NA provides a theoretical basis for clinical treatment. This article reviews the previous research of our research group and the current situation of domestic and foreign research.

Keywords: neoatherosclerosis; vascular smooth muscle cells

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1 INTRODUCTION

Neoatherosclerosis (NA) serves as the underlying pathological basis for complications such as in-stent restenosis (ISR) and in-stent thrombosis (IST) but also acts as the primary impediment to interventional therapy. Pathologically, NA is primarily characterized by the buildup of lipid foam cells in the neointima, sometimes accompanied by necrotic core formation or calcification. Studies on the underlying mechanisms suggest that endothelial structural insufficiency and dysfunction resulting from stent-related mechanical or chemical injury are the initial triggers for NA, although the specific pathological mechanisms and treatments involved remain unclear.

With an increasing incidence rate, cardiovascular diseases have become a major public health issue worldwide. According to the China Cardiovascular Health and Disease report 2022, there are 330 million cases of cardiovascular disease in China, with 2 out of every 5 deaths attributed to cardiovascular disease. Coronary revascularization therapy has greatly improved the condition and prognosis of these important cardiovascular diseases. Typical procedures include percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). However, post-PCI complications such as IST, ISR, and, more significantly, NA associated with the widespread use of drug-eluting stents have become the main residual risk factors for adverse cardiovascular outcomes after intervention. Similar to the progression, regression, and occlusion of arterial atherosclerosis in bypass grafts after CABG, NA within the stent has also increasingly become a key remaining risk factor for clinical cardiovascular events after coronary intervention. However, research on the core pathogenesis of this disease is still lacking, and sufficient and effective preventive and treatment measures are lacking[1–3].

For atherosclerosis, which has undergone a century of research and exploration, significant progress has been achieved in understanding various mechanisms involved in its formation, such as lipid infiltration, endothelial cell dysfunction, inflammation driven by oxidized lipids, and the migration and proliferation of vascular smooth muscle cells[4–6]. The development of atherosclerosis can be described as a lipid-driven inflammatory response in blood vessels[7]. Despite the fruitful achievements in basic research, the current stage of clinical practice for the treatment of atherosclerosis is still limited to lipid-lowering, anticoagulation, and intervention and surgical treatments. In reality, there is still a lack of translation of basic research findings into clinical applications. Unlike in native atherosclerosis, the lipid necrotic core and outer fibrous cap of the NA within the stent are often atypical (figs. 1 and 2). Unlike native atherosclerosis, which requires slow development over many years or even decades, NA within the stent is more likely to occur within a relatively short time after drug-coated stent implantation,

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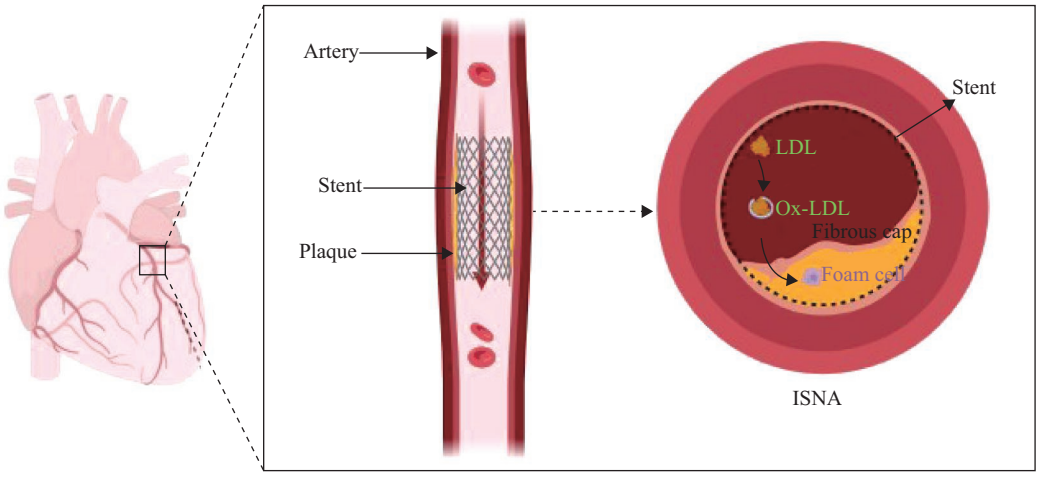

Fig. 1 Schematic diagram of stent implantation and NA formation (created using BioRender.com)
ISNA: in-stent neoatherosclerosis; LDL: low-density lipoprotein; Ox-LDL: oxidized low-density lipoprotein

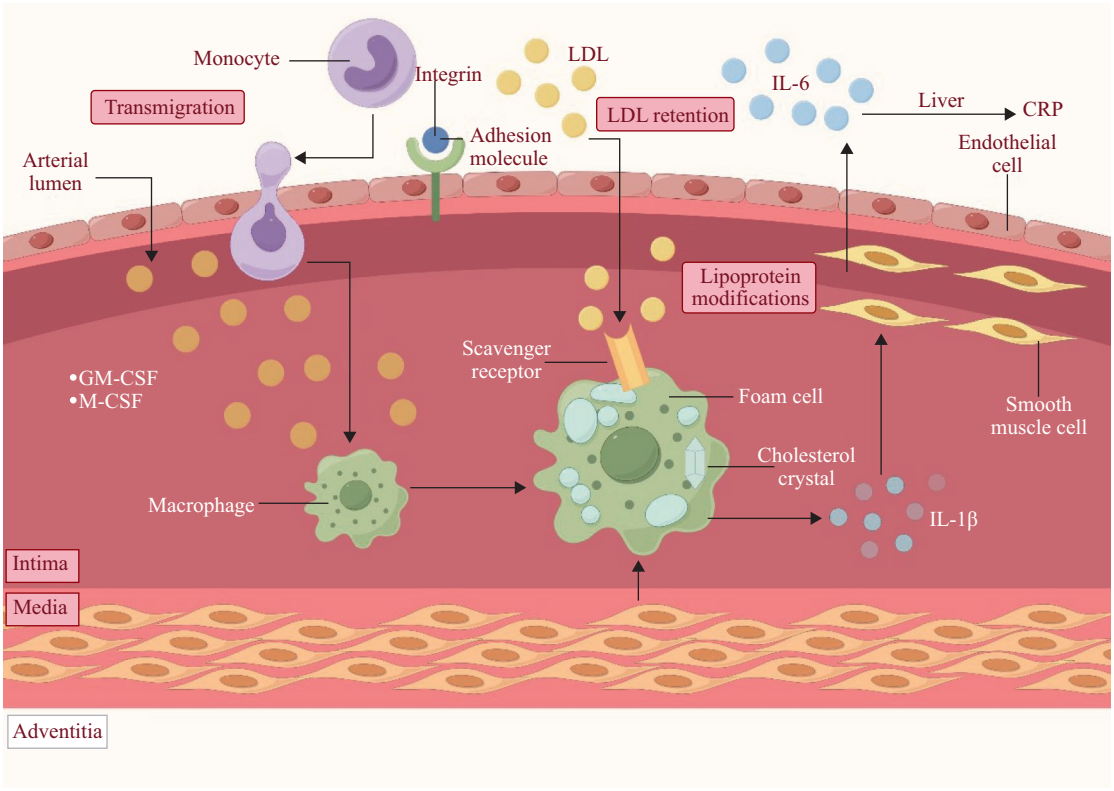

Fig. 2 The mechanism of atherosclerosis (created by Figdraw)
LDL: low-density lipoprotein; CRP: C-reactive protein; GM-CSF: granulocyte-macrophage colony stimulating factor; M-CSF: macrophage colony-stimulating factor; LDL: low density lipoprotein; IL-6: interleukin 6; IL-1β: interleukin 1β

often within a few years after stent placement. It manifests as myocardial ischemia caused by lumen stenosis or late and very late stent thrombosis caused by plaque rupture. According to the pathological analysis of the NA within the stent, the occurrence and development of the NA within the stent are related to the repair of vascular injury after coronary intervention, sustained endothelial loss or dysfunction caused by drug-coated stents, direct and rapid infiltration of lipids into the vascular smooth muscle layer under the lack of endothelial barrier protection, and a persistent inflammatory response caused by a foreign body reaction to the stent. NA has become an urgent clinical need in the era of coronary artery intervention, but its specific mechanism requires further investigation.

This paper systematically summarizes the influencing factors of NA, pathological characteristics, pathogenesis, and existing problems, in conjunction with the latest research progress. The aim is to enhance medical staff's understanding of NA and provide a theoretical basis for future research on the subject.

2 NA PATHOGENIC FACTORS

Most patients do not experience obvious recurrence of atherosclerosis after surgery or stent implantation at atherosclerotic lesion sites. A total of 512 patients

who underwent optical coherence tomography before percutaneous coronary intervention for second-generation drug-eluting stent restenosis were included. The study revealed that the prevalence of NA in this group was 28.5% (146 patients out of 512)[8]. However, interventional treatment inevitably causes vascular injury and subsequent inflammatory reactions, and the presence of a stent serves as a long-term stimulus for inflammation. Additionally, in the real world, lipid-lowering therapy after stent implantation is not ideal for achieving treatment goals. Nevertheless, some patients still continue to experience recurrent atherosclerotic cardiovascular events despite acceptable lipid control. These patients can benefit from more intensive lipid control. According to the current clinical consensus, patients with multivessel disease, repeated coronary events, recent myocardial infarction, and other high-risk factors are considered to have extremely high-risk atherosclerotic cardiovascular disease. These patients are given potent cholesterol-lowering medications, including PCSK9 inhibitors (proprotein convertase subtilisin/kexin type 9 monoclonal antibodies, PCSK9i), HMGCoA reductase inhibitors (statins) that inhibit hepatic cholesterol synthesis, and other drugs to promote liver absorption of low-density lipoprotein (LDL) cholesterol. The treatment aims to reduce plasma LDL cholesterol levels by at least 50% and achieve a level of 1.4 mmol/L, or even lower than 1.0 mmol/L, which is considered the cholesterol level of a newborn[9]. This intensified lipid control approach indeed improves clinical prognosis, but its benefits mainly come from the treatment of atherosclerotic plaques in nonstented vascular segments. This cannot explain the phenomenon of faster progression of newly formed atherosclerosis at the stent implantation site compared to the original lesion *in situ* coronary arteries, which is frequently observed. Studies have shown that inherent atherosclerotic plaques at lesion sites play an important role in the development of in-stent neointimal hyperplasia[10]. Andreou *et al* found through intravascular ultrasound (IVUS) that the reduction in the volume of primary atherosclerotic plaques and the decrease in the occurrence of new intima were correlated[11], indicating the significant role of primary atherosclerotic plaques in in-stent neointimal hyperplasia.

Previous studies have shown that there are sex differences in the occurrence of atherosclerosis. Yuan *et al* demonstrated that among patients with ISR who received drug-eluting stents (DESs), the incidence of in-stent neointimal hyperplasia was significantly lower in female patients than in male patients. Additionally, the occurrence rates of lipid-rich neointima and calcified neointima were both lower in female patients than in male patients. Male patients exhibited greater vulnerability of the neointima than female patients. Blood lipid levels and inflammation are involved in the development of neointimal atherosclerosis[12]. However, the specific pathogenesis remains to be explored.

Multiple factor logistic regression analysis revealed that the eGFR, time from PCI to ISR, and DES were correlated with NA. Furthermore, compared to BNS, there is a greater correlation between in-stent restenosis and the NA in DES stents[13]. Chronic kidney disease, LDL > 70 mg/dL, and the duration of stent implantation are also independent predictive factors for NA[14].

In addition, the hemodynamics of the stent implantation segment also contributes to the occurrence of NA. The blood flow in the stent implantation area becomes disordered, leading to the activation of regenerative endothelial cells and the expression of adhesion molecules. Subsequently, monocytes adhere to endothelial cells, migrate to the subintima, and transform into macrophage-like foam cells, participating in the occurrence and development of NA. Endothelial shear stress (ESS) participates in the formation of vulnerable plaques in the NA by regulating the proliferation of new intima within the stent and regulating the inflammation of the new intima[15].

3 NA PATHOLOGICAL CHARACTERISTICS

ISR was once a challenge during the era of simple percutaneous coronary intervention (PTCA) and bare-metal stents, with the core pathogenesis being negative vascular remodeling caused by intimal fibroproliferation. With the advent of the DES era, the rate of ISR has significantly decreased. The widespread use of DESs has led to an increase in late thrombotic events following stent implantation due to delayed endothelialization prolonging the duration of dual antiplatelet therapy after surgery. With the development of DES materials, polymer coatings, manufacturing processes, improvements in stent implantation technology, and standardized applications of antiplatelet drugs, the incidence of IST has greatly decreased[16]. However, while the above two problems are being solved, with the widespread use of DESs, NA is becoming an increasingly important clinical issue in coronary intervention treatment. Although the new generation of DESs has good clinical effects, the incidence of NA after stent placement is similar between the new generation and the first generation of DESs[17]. NA within the stent is closely related to late thrombotic events after stent placement[18, 19]. The present study showed that the NA had a more diffuse pattern in the bare metal stent (BMS) group than in the DES group[20]. NA occurs years after the implantation of bare metal stents but occurs quickly after DES implantation[18]. This may be due to the delayed healing and inflammatory effects caused by the antiproliferative drugs and polymers in the DES.

The neointima is defined as the tissue between the lumen profile and the stent profile. The calcified neointima has a distinct contour, with a poor signal area and clear boundaries. Neointimal atherosclerosis is defined as lipid or calcified neointima, where the neointima is diffusely thickened and atherosclerotic changes can be observed[12, 14, 20, 21]. NAs can be classified as type Ⅰ thin-cap, type Ⅱ thick-cap, or type Ⅲ peristaltic based on morphology. Among them, type Ⅰ is more common in patients with DESs[22].

NA histology is characterized by the aggregation

of abundant foam-like macrophages in the neointima, which may or may not be accompanied by necrotic cores or calcification. These foam-like macrophages gradually migrate to the intima, leading to the formation of thin-cap fibroatheromas. The presence of a thin fibrous cap in the NA plaque increases the likelihood of complications such as plaque rupture and thrombosis. The neointima is also prone to calcification, with significant variations in calcification morphology, ranging from microcalcification caused by the apoptosis of foam-like macrophages to plaque-like calcification caused by extracellular matrix and collagen calcification[23].

There are many differences in atherosclerosis after the implantation of DESs and BMSs, mainly in terms of their components, formation events, progress, and prognosis. At present, the main research methods for treating NA are IVUS and optical coherence tomography (OCT), which are used to study neointimal characteristics (table 1).

ISR is mainly related to the proliferation of endometrial fibrous tissue in the stent implantation area. The use of DESs has significantly improved this problem. However, in-stent NA is characterized by atherosclerotic plaques rich in cholesterol lipids and foam cells. In addition to causing vascular lumen restenosis, plaque rupture and thrombosis can also occur, leading to acute coronary events such as unstable angina, acute myocardial infarction, and sudden cardiac death. Unlike in native atherosclerosis, the lipid necrotic core and outer fibrous cap of the NA within the nonatherosclerotic stent are often atypical and more often manifest as clusters of lipid-rich foam cells around the stent struts. The thickening of the outer endothelium of the lesion tissue is not obvious, and it is often directly derived from the proliferation of vascular smooth muscle cells. Similar to native atherosclerosis, in-stent NA (ISNA) also has unstable morphological characteristics, such as a large necrotic core, plaque rupture and hemorrhage, thin fibrous cap, etc. Unlike native atherosclerosis, the development of ISNA is more rapid, often occurring within a few years or months after stent implantation[23] (table 2).

4 NA PATHOGENESIS

Many studies and the literature have explored the mechanism of NA within the stent[24, 25], mainly focusing on two factors. One factor is the long-term loss and incomplete coverage of endothelial cells after the placement of drug-eluting stents, which causes the loss of barrier function against lipid infiltration and anti-inflammatory, antithrombotic, and circulation-improving protective effects of endothelial cells, providing a basis for the development of atherosclerosis. Biopsy of 299 patients revealed that the average time for the formation of neointimal plaque after DES placement was 420 days, which was significantly shorter than the average time of 2160 days for BMSs[18]. A previous histological examination of 143 biopsy specimens revealed that NA occurred approximately 4 months after DES placement[26]. Another factor is that some individuals still have high levels of LDL cholesterol after surgery[27], and hyperlipidemia promotes the occurrence of NA at the stent placement site. In summary, these two factors are important factors for NA; that is, if lipid control is not good under conditions of endothelial loss, it will promote lipid deposition in damaged vessel walls and thus the formation of NA.

Endothelial injury is considered the initiating factor in the pathogenesis of NA. Studies have shown that the expression level of endothelial nitric oxide synthase decreases after DES implantation in the implanted segment of the blood vessel. Compared with those in bare metal-, sirolimus- and tacrolimus-eluting stents, endothelial function rather than endothelial restoration is altered in paclitaxel-eluting stents[30]. Therefore, sirolimus and paclitaxel-eluting stents can inhibit endothelial cell proliferation and cause endothelial dysfunction. Persistent endothelial deficiency caused by drug-coated stents allows LDL particles to directly infiltrate the vascular media. Due to endothelial dysfunction, antioxidant capacity and free radical scavenging activity of these materials

Table 1 The difference in the NA between DES and BMS

Parameters	DES	BMS
Constituent component	VSMCs component is less	VSMCs[28]
Formation time	Short (about 100 days)	Long (about 900 days)[18]
Incidence of lipid-containing plaque	Hing	Low[29]
Lipid core load index	High	Low
Lipid core load density	High	Low
NA types	Many thin-cap	Less thin-cap[30]

DES: drug-eluting stent; BMS: bare metal stent; VSMCs: vascular smooth muscle cells

Table 2 Differences between atherosclerosis patients and NA patients

Parameters	Atherosclerosis	Neoatherosclerosis
Formation time	Long	Short
Constituent component	Foam cell	Foam cell
Fibrous cap	Thin	Thin, atypical
Necrotic core	Big, deep	Big, superficial
Early pathological changes	Endothelial thickening	Endothelial thickening with proliferation of VSMCs
Fibrous calcified plaque	Very common	Common, especially in the DES

VSMCs: vascular smooth muscle cells

decrease, and lipid particles are more likely to oxidize to form oxidized-LDL (Ox-LDL) at the stent location and deposit on the vessel wall, which is then phagocytosed by vascular smooth muscle cells to form foam cells and lipid plaques, further leading to neoatherosclerosis formation. After DES implantation, the anti-proliferative drugs on the stent surface impede the integrity of the endothelial cells, leading to leakage in endothelial cell connections and accelerating lipid deposition, thereby accelerating NA formation. Additionally, chronic inflammation caused by macrophage migration and foam cell formation also plays a key role in NA[31].

In-stent NA is a type of atherosclerosis with a large number of oxidized lipid residues in the stent area. Its pathological characteristics differ significantly from those of primary atherosclerosis. NA plaques grow around the residual oxidized lipid core and stent strut clusters and are primarily characterized by smooth muscle cells engulfing lipids to form foam cells. This is related to vascular injury repair, endothelial damage caused by drug stents, and foreign body inflammation reactions of the stent, but the core mechanism is related to the fact that residual oxidized lipids at the stent site and circulating lipids are more likely to undergo oxidative modification and directly infiltrate into the middle layer of vascular smooth muscle after endothelial barrier injury. The existing strategy of simply limiting the reduction in circulating LDL has limited inhibitory effects on the NA within the stent. Only effective removal of Ox-LDL in the stent area may fundamentally inhibit the formation of in-stent NA. Our research group has been committed to atherosclerosis research for a long time and has now developed a gene agent that can transfer Ox-LDL to the liver for metabolic clearance, i.e., the AAV8-TBG-LOX-1 gene agent. LOX-1 is stably expressed in liver tissue within 4 weeks and can engulf and clear Ox-LDL[32]. Further research confirmed that ectopic expression of the LOX-1 receptor in the liver can significantly inhibit the progression of late atherosclerotic plaques by clearing Ox-LDL[33]. Next, by establishing an $Apoe^{-/-}$ mouse NA model, it was found that the ectopic expression of LOX-1 in liver cells clears Ox-LDL, alleviates the phenotypic transition of VSMCs, and alleviates NA; these effects are unrelated to LDL-lowering treatment. Further mechanistic studies revealed that ectopic expression of LOX-1 in the liver protects VSMCs from phenotypic transformation and wire injury-induced carotid atherosclerosis by upregulating ALOX15[34]. This provides a new unique idea for the treatment and prevention of NA.

5 CURRENT ISSUES

At present, there are relatively few studies on NA, and the literature is quite outdated. Therefore, a large amount of basic research and clinical research is urgently needed to explore the pathogenesis of NA. The development of atherosclerosis is a process in which lipids continuously deposit, oxidize, and trigger the inflammatory immune system, leading to lipid phagocytosis and inflammatory proliferation. Naturally, controlling lipid levels is a key measure for suppressing atherosclerosis, and existing clinical research and practice have fully confirmed this effect. From cholesterol synthesis inhibitors such as statins to cholesterol absorption inhibitors, PCSK9 inhibitors, and small interfering RNA (siRNA) drugs, lipid levels have been effectively controlled. However, these are lower free LDL-cholesterol levels and their benefits are mainly derived from their therapeutic effect on atherosclerotic plaques in nonstent vascular segments; it is difficult to specifically remove Ox-LDL. Therefore, there is an urgent need to develop targeted Ox-LDL drugs for the treatment and prevention of NA.

6 SUMMARY AND OUTLOOK

NA is a type of atherosclerosis characterized by more residual oxidized lipids within the stent area. Its pathological features differ significantly from those of native atherosclerosis. The NA plaque grows around the residual oxidized lipid core and the stent strut cluster, dominated by smooth muscle cells engulfing lipids to form foam cells. This is related to vascular injury repair, drug stent-induced endothelial injury, and the stent foreign body inflammatory response. However, the more critical mechanism is the easy oxidation modification and direct infiltration into the middle layer of vascular smooth muscle after endothelial barrier injury caused by residual oxidized lipids at the stent site and circulating lipids. The existing strategy of simply reducing circulating LDL to the limit has limited inhibitory effects on in-stent neoarteries. Only effective removal of Ox-LDL in the stent area may fundamentally inhibit the formation of the NA. With the widespread application of DESs, NA has become an urgent problem to be solved in current clinical practice. Although many studies on NA have been conducted, the pathogenesis of NA is still unclear. Therefore, exploring the pathogenesis and pathological characteristics of NA in depth can lay a theoretical foundation for the development of new stents in the future. There is a long way to go before NA can be prevented and treated.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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