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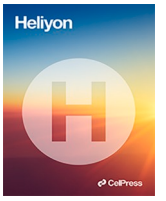

Research article

The many roles of cathepsins in restenosis☆

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ABSTRACT

Drug-eluting stents (DES) and dual antiplatelet regimens have significantly improved the clinical management of ischemic heart disease; however, the drugs loaded with DES in clinical practice are mostly paclitaxel or rapamycin derivatives, which target symptoms of post implantation proliferation and inflammation, leading to delayed re-endothelialization and neo-atherosclerosis. Along with the treatments already in place, there is a need for novel strategies to lessen the negative clinical outcomes of DES delays as well as a need for greater understanding of their pathobiological mechanisms. This review concentrates on the function of cathepsins (Cats) in the inflammatory response and granulation tissue formation that follow Cat-induced damage to the vasculature scaffold, as well as the functions of Cats in intimal hyperplasia, which is characterized by the migration and proliferation of smooth muscle cells, and endothelial denudation, re-endothelialization, and/or neo-endothelialization. Additionally, Cats can alter essential neo-intima formation and immune response inside scaffolds, and if Cats are properly controlled in vivo, they may improve scaffold biocompatibility. This unique profile of functions could lead to an original concept for a cathepsin-based coronary intervention treatment as an adjunct to stent placement.

1. Introduction

Cardiovascular disease (CVD) poses a substantial threat to human health in contemporary society. The global incidence rate of CVD has risen dramatically, due in part to the abandonment of traditional diets and lifestyles for more calorie-rich, sedentary alternatives.

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Despite the considerable reduction in cardiovascular disease (CVD) mortality achieved through percutaneous coronary intervention (PCI) involving stent implantation and double antiplatelet therapy, it is something remarkable that adverse effects such as in-stent restenosis (ISR) and thrombosis continue to limit CPI therapy. Additionally, it should be noted that stent design and supplementary treatment methods have become more varied compared to previous approaches [1–3]. The stenting-related complications following stenting are caused by a combination of mechanical damage to the medial wall of the vessel (e.g., when the entire endothelium is stripped or compressed or plaque is removed) and the inflammation-induced damage associated with smooth muscle cells (SMC) proliferation, thrombosis, and renewed or *de novo* atherosclerotic processes [4–6]. To address the clinical problems of restenosis after stenting, various coping strategies have been developed, including drug-coated stents, the use of anti-platelet aggregation drugs, and immunotherapy. However, these treatment options have therapeutic limitations (bleeding, slow onset of action, residual metal foreign bodies, etc.), and therefore new treatment strategies are needed [1,7–9].

Cysteine protease cathepsins have traditionally been considered lysosomal restricted proteases that modulate the proteolysis of unwanted proteins. It was once believed their protein-degrading function required the acidic pH of the intracellular environment [10, 11]. Nevertheless, certain Cats (cathepsins S, K, G, B, and L) also exhibit activity within the neutral extracellular milieu, engaging in a multitude of biological mechanisms related antigen transmission, inflammatory conditions, and immunity, along with extracellular matrix modulation. Consequently, these Cats play a significant role in the initiation and progression of a diverse range of pathological conditions, including atherosclerosis, cardiac infarction, arthritis, lupus, and cancer [10–15].

Cats have been implicated in numerous complications following stent implantation via their roles in monocyte adhesion, thrombosis, inflammation, immunity, extracellular matrix remodeling, and vascular smooth muscle cell (VSMC) proliferation and migration [16–20]. Accumulating evidence documented that the multifunctional Cats involved in cardiovascular disease initiation and progression in animals and humans [21]. Cats have also been applied to target for the treatment of the inflammatory cardiovascular disease [16,18,22–26]. In addition, the research findings on Cats have made possible noteworthy advances in Cats as a useful biomarker for cardiovascular diseases [21,27]. This review attempts to summarize the achievements regarding the roles of Cats in these research fields, especially restenosis and thrombosis.

2. Cats are involved in all phases of stent-related restenosis

After balloon angioplasty and endovascular stent implantation, the platelet activation and thrombosis, activation of chemokines and cytokines, vascular VSMC proliferation and migration facilitates the neointimal formation, leading to vascular restenosis. Neointimal formation is a significant pathological cause of myocardial infarction following stent implantation. In recent years, research has revealed that Cats play significant roles during this post-procedure period, as shown in Fig. 1.

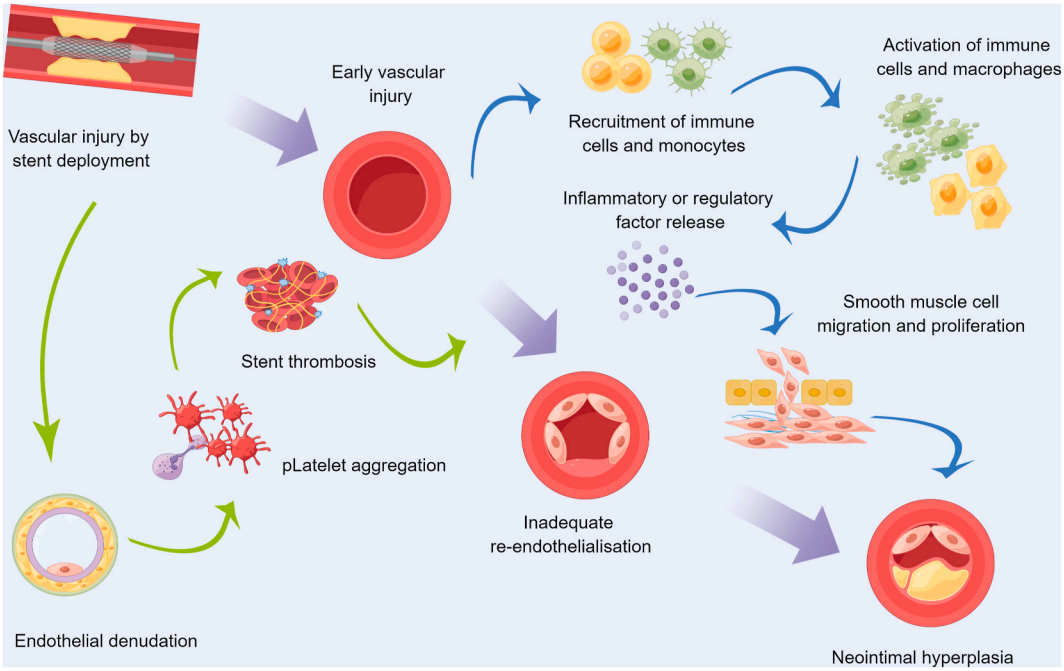

Fig. 1. Cats play roles in the occurrence and progression of restenosis following stent implantation. After implantation of the stent or balloon into the blood vessel, the vascular endothelial cells are largely or completely evacuated from the implantation site. With platelet activation, local microthrombosis encompasses the site of the injury. Numerous Cats are implicated in this process, particularly in platelet activation and thrombosis. In addition, Cats can attract immune cells, promote the release of inflammatory factors, and play important roles in VSMC proliferation, migration, and cell-type transformation: in short, they promote the formation of a neointima, with the ultimate result of restenosis.

2.1. The function of cats in the earliest phases of stent restenosis

The early phases following stent deployment are accompanied by partial destruction of endothelial cells (ECs). Due to the exposure of the internal architecture and the activation and aggregation of blood platelets induced by the presence of a foreign body in the vascular conduit, thrombus formation commences. When activated monocytes or immune cells infiltrate the site of vascular injury, they begin to secrete large amounts of cytokines, promoting changes in local endothelial cells that can result in thrombosis.

2.1.1. Role of cats in endothelial cell denudation after stenting

Denudation of endothelial cells is typically a significant problem when a vascular stent is implanted. Due to the hemodynamic changes, vascular fluid pressure alterations, and localized inflammatory cell infiltration and cytokine release, endothelial cells adjust

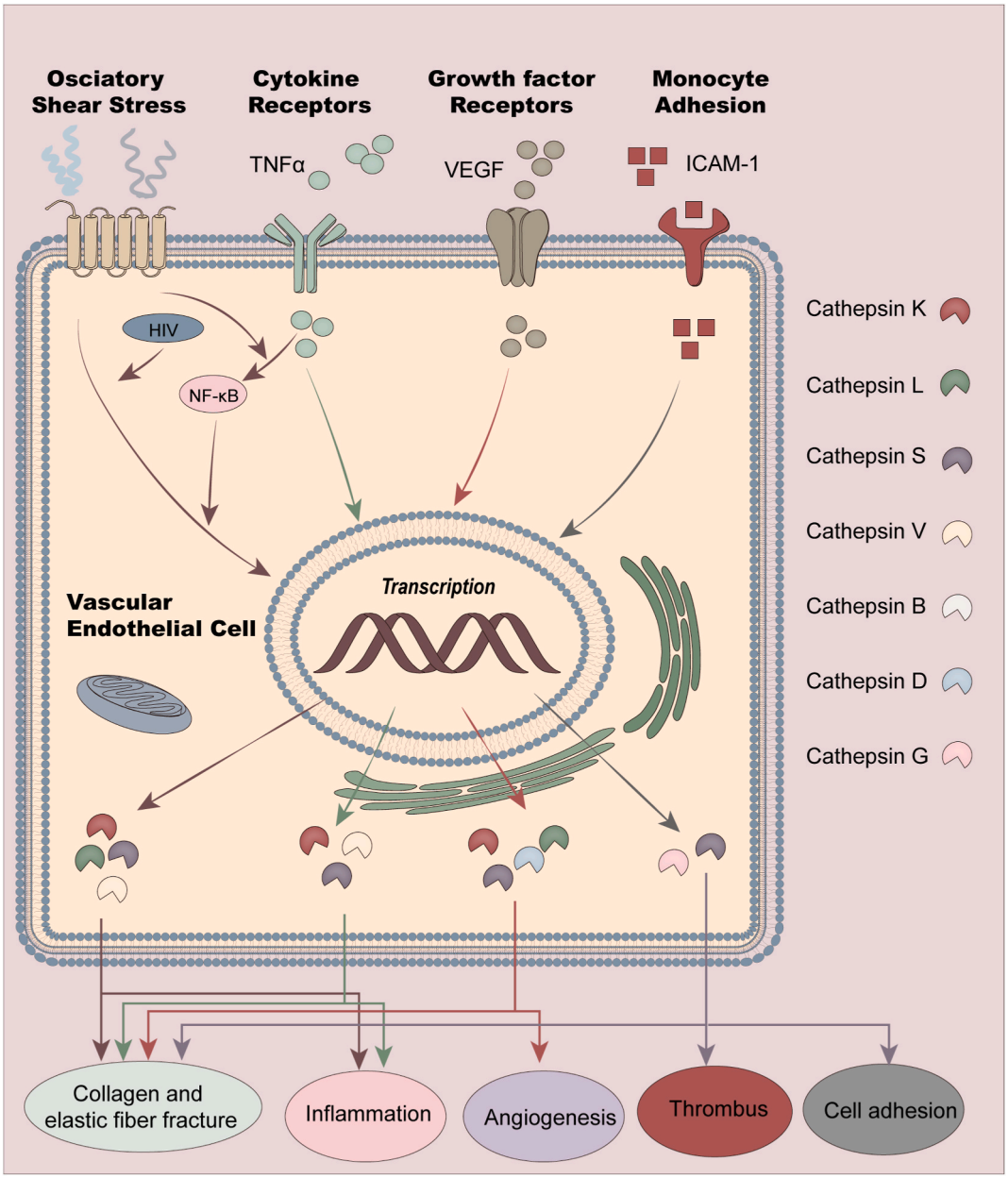

Fig. 2. Endothelial cells are influenced by a variety of factors and participate in a variety of biological processes. Endothelial cells produce a variety of Cats after stent implantation due to the foreign-body destruction of the vascular endothelium, local hemodynamic changes (oscillatory stress), and the release of cytokine receptors (TNF, VEGF, ICAM-1). These Cats are then involved in collagen and elastic fiber fracture, inflammation, angiogenesis, thrombosis, and cell adhesion.

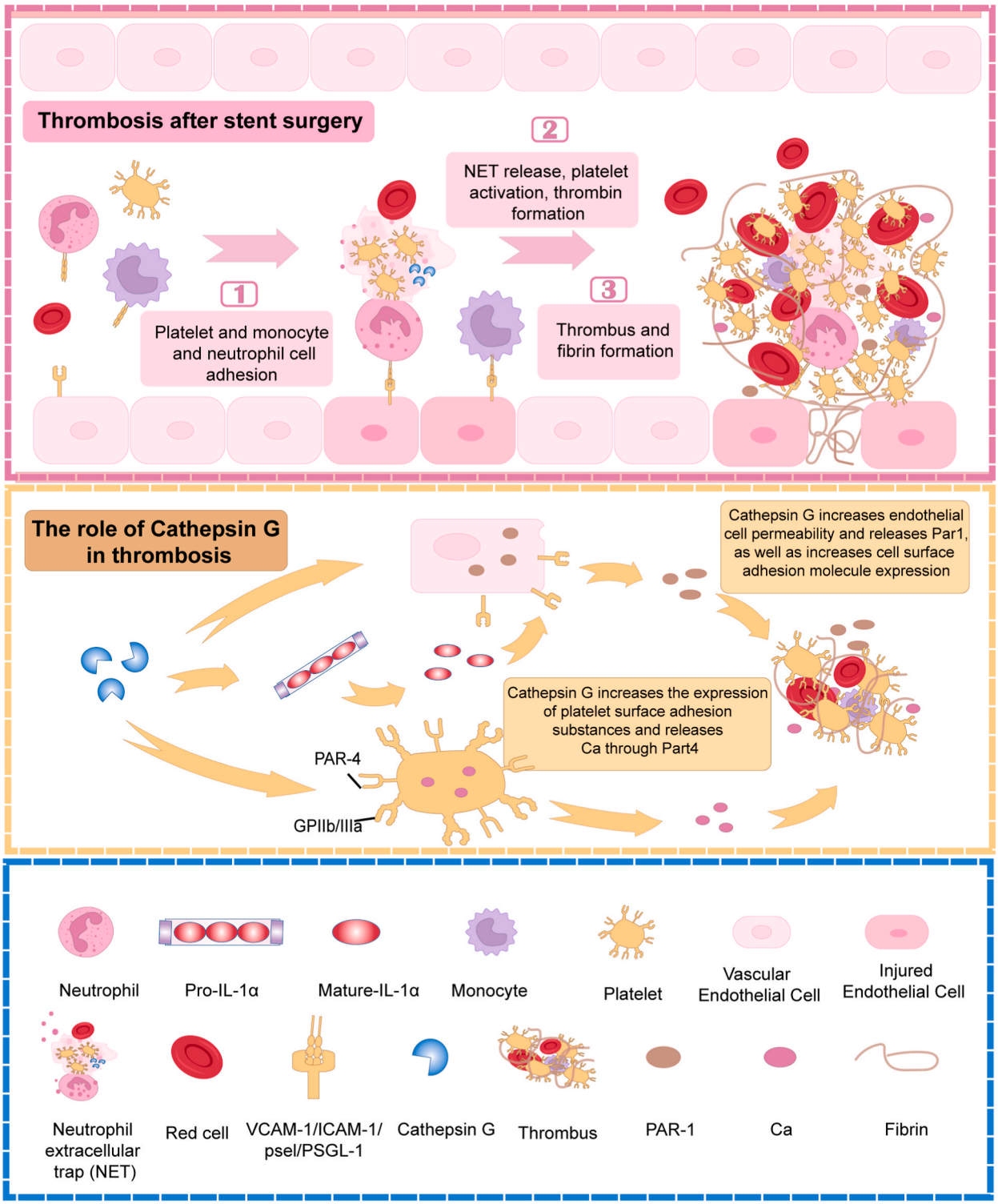

Fig. 3. Cats contribute to thrombus formation primarily by influencing endothelial cells and platelets. Cats stimulate the formation of thrombi by activating endothelial cell permeability to release PAR-1 or by increasing the expression of cell surface adhesion molecules in platelets and endothelial cells following stenting. Thrombus formation involves the expression of PAR-4/GPIIb/IIIa adhesion molecules on the surface of activated platelets.

by secreting specific Cats that decompose extracellular collagen and elastic lamina, and participate in extracellular matrix remodeling, as shown in Fig. 2.

Shear stress constitutes a tangential mechanical force that fluctuates at regular intervals in response to the heart's pumping action. Variations in the amplitude and frequency of shear stress within arteries are linked to a wide variety of processes in cardiovascular wellness and disease [28,29]. The expression of Cats is inhibited and the vascular morphology is preserved when the shear force is stable [30]. Due to the obstruction of blood flow or changes in discharge direction, pockets of low pressure or oscillating shear stress are generated at vascular bifurcations, atherosclerotic plaques, or vascular stent sites, inducing the expression of Cats that participate in vascular remodeling. Philip and colleagues observed that the disturbance of blood flow and the presence of tumor necrosis factor alpha (TNFα) led to an increase in the expression of CaK and V in endothelial cells after stent implantation. Conversely, the application of vascular protective shear stress appeared to mitigate the activation of the JNK/c-jun signaling pathway, which in turn limited the activation of CatK by inhibiting the NF-κb pathway [28]. In an experiment with diabetic rats, it was discovered that laminar flow decreased the activity of CatL produced by endothelial cells, decreased the conversion of latent heparinase into active heparinase, and affected lipoprotein lipase (LPL), thereby influencing myocardial cell metabolism [29]. In an in vitro experiment, oscillating shear stress increased CatK expression in human atherosclerotic endothelial cells [31]. Furthermore, the presence of fluid shear stress (FSS) induces the secretion of CatB by neutrophils, resulting in a specific anti-adhesion impact on endothelial cells mediated by Mac1 [30]. CatK, which is known to have a notable impact on the process of inflammatory vascular remodeling, can be induced by various factors such as HIV proteins, low pressure, or oscillatory stress [32].

The detection of tumor necrosis factor alpha (TNFa) in the bloodstream plays a significant role in the activation of Cat. Specifically, TNFa stimulates vascular endothelial cells to produce CatK and CatV, which have been associated with arterial remodeling as a result of prolonged inflammation [33]. In an in vitro study, human aortic epithelial cells at confluence were subjected to stimulation using TNFα or THP-1 macrophage cocultures. The findings revealed that the activity of CatV was enhanced by the presence of CatK, while the administration of SP6000125 effectively inhibited the up-regulation of both CatK and CatV activities in the endothelial cells [28]. Furthermore, in a murine model of FeCl (3)-induced thrombus development during surgical procedures, the pro-inflammatory cytokine TNFα was shown to enhance the expression of CatS, leading to heightened vascular inflammation and enhanced thrombus formation in the presence of sustained stress [34]. These experiments demonstrated that during the early phase of vascular remodeling, inflammatory cytokines can upregulate Cat activity via the JNK signaling axis and monocyte–endothelial cell interactions [35].

Recent multicenter studies have demonstrated that by degrading the extracellular matrix and interacting with VEGF, Cats play important roles in angiogenesis [36–40]. In one study, it was discovered that CatK gene knockout could impair the regeneration of blood vessels in old mice; another report showed that CatL levels and tumor blood vessel regeneration are directly and closely related [36,37]. Together, these studies indicate that Cats might contribute to the process of blood vessel regeneration, although the specific mechanism remains uncertain. According to a mechanistic study, VEGF levels impact CatK in response to hypoxia via the Notch1 pathway, and thereby influence angiogenesis. Additionally, it has been reported that VEGF influences the participation of CatD in angiogenesis [38,39]. In a pharmacological investigation, it was shown that inhibitors of CatS have a significant involvement in the process of angiogenesis, particularly in the presence of VEGF [41].

Cats are also known to play significant roles in the processes of thrombus formation and monocyte adherence to the vascular wall. Research investigations have provided evidence that ICAM-1 not only facilitates monocyte adhesion mediated by CatG, but also plays a critical role in thrombosis mediated by Cats [,42].

2.1.2. What is the connection between cats and thrombosis?

In the preceding chapter, we discussed the function of cathepsins in the process of endothelial cell denudation during stenting, as well as the subsequent delayed re-endothelialization. It is well-known that the most serious problem with DES is not restenosis caused by proliferation, but late thrombosis, which has a very high mortality rate. Thrombosis, the most lethal consequence resulting from delayed re-endothelialization, has garnered significant clinical focus. In recent decades, there has been a significant amount of research focused on investigating the involvement of Cats in arterial wall remodeling. However, there has been very limited findings regarding their contribution to thrombosis. Our recent investigation has focused on the interaction between thrombus and Cats, as schematized in Fig. 3.

In a clinical investigation involving the development of aortic aneurysms during surgical procedures, the aorta and blood clots from organ donors were utilized as control specimens. The findings of this study revealed a significant upregulation of CatD and CatL activities within the aneurysm of the aortic wall alongside peripheral thrombus. Conversely, the expression of cysteine Cat inhibitor was observed to be relatively low [43]. This indicates a link between thrombi and Cats. However, while these early researches have shown that Cats are associated with thrombosis, the systematic mechanism has not been clarified.

A review by Burster et al. has shown that CatG accounts for the majority of articles on Cats and blood vessels, and provides a summary of the varied roles of CatG in thrombosis [44]. In an earlier report by LaRosa and colleagues, CatG was shown to enhance the production of p-selectin, glycoprotein IIb/IIIa complex, and glycoprotein IV on the surface of platelets. These proteins are known to be involved in neutrophil binding, fibrinogen receptor activity, and thrombus-reactive protein receptor activity, respectively [45]. Multiple studies have provided evidence indicating that when the extent of vascular de-endothelialization surpasses 55 %, the presence of CatG has a notable impact on the structure of endothelial cells. This effect leads to an expedited development of blood clots by augmenting the permeability of endothelial cells in the arteries and facilitating the binding of PAI-1 to the extracellular matrix [46]. In addition to its effects on vascular endothelial cells, purified CatG induces platelet calcium mobilization, thromboxane formation, serotonin release, platelet aggregation, and p-selectin expression [47]. CatG is capable of cleaving plasma zymogen factor V and factor X and activating platelets via PAR-4, resulting in calcium mobilization [48]. Moreover, it has been shown that neutrophil extracellular

traps (NETs), which are strands of DNA found outside of cells, play a role in the activation of endothelial cells (ECs) and enhance the formation of blood clots through the combined effects of interleukin-1 (IL-1) and cathepsin G (CatG) [49]. The expression of CatG occurs in cellular environments where endothelial cells undergo injury, leading to the activation of platelets and subsequent expression of p-selectin [48]. Polymorphonuclear leukocytes (PMNs) then attach to p-selectin via glycoprotein ligand-1. Additionally, Mac-1, an integrin ligand, facilitates increased adhesion and tighter interaction between endothelial cells [48]. PMNs undergo a process of differentiation, whereby they transition into macrophages via the mechanism of blood vessel distortion [48].

Collectively, the above evidence suggests that CatG plays a pivotal role in the development of thrombosis. Indeed, a study using a mouse model indicated that CatG knockout can substantially reduce thrombosis [50]. Furthermore, the use of a protein kinase C (PKC) inhibitor has been shown to effectively impede the enzymatic activity of CatG and diminish platelet responses, including aggregation of platelets, morphological alterations, and the release of dense granules. Consequently, this inhibition mechanism holds potential as an antithrombotic intervention [51]. In addition, a high-resolution imaging study disclosed that the binding of CatG to thrombospondin-1 is tight and reversible, and occurs in sufficient proximity to the active site of CatG to interfere with the binding of protein substrates and platelets for an antithrombotic effect [52]. Heparin inhibits neutrophil-derived CatG-induced platelet activation, further implicating CatG in the thrombotic process [53]. In our recent experiments using the mouse FeC13 model of carotid artery thrombosis, we showed that CatS can reduce vascular inflammation, oxidative stress, and apoptosis by reducing vascular inflammation, indicating that CatS plays a critical role in these processes []. This key evidence of a critical role of Cats in thrombosis after vascular injury may inspire new therapeutic approaches for the complications of thrombosis after stenting due to delayed endothelial healing.

2.2. *The midterm roles of cats following stent implantation*

2.2.1. *Role of cats in oxidative stress*

Oxidative stress, a concept introduced in 2017 by Helmut Sies, refers to an imbalance between the generation of oxidants and the protective mechanisms of antioxidants, which may lead to harm to biological systems [54]. Oxidative stress is the main cause of the transformation of LDL cholesterol into oxidized-LDL (OxLDL), which plays a critical role in triggering and advancing the inflammatory response and attracting white blood cells to the site of injury [55]. This process contributes to the progression of atherosclerosis by activating SMCs and reducing the availability of nitric oxide (•NO) [56]. Oxidative stress may disrupt several signaling pathways and impact different biological processes by mechanisms such as altering proteins, stimulating inflammation, triggering apoptosis,

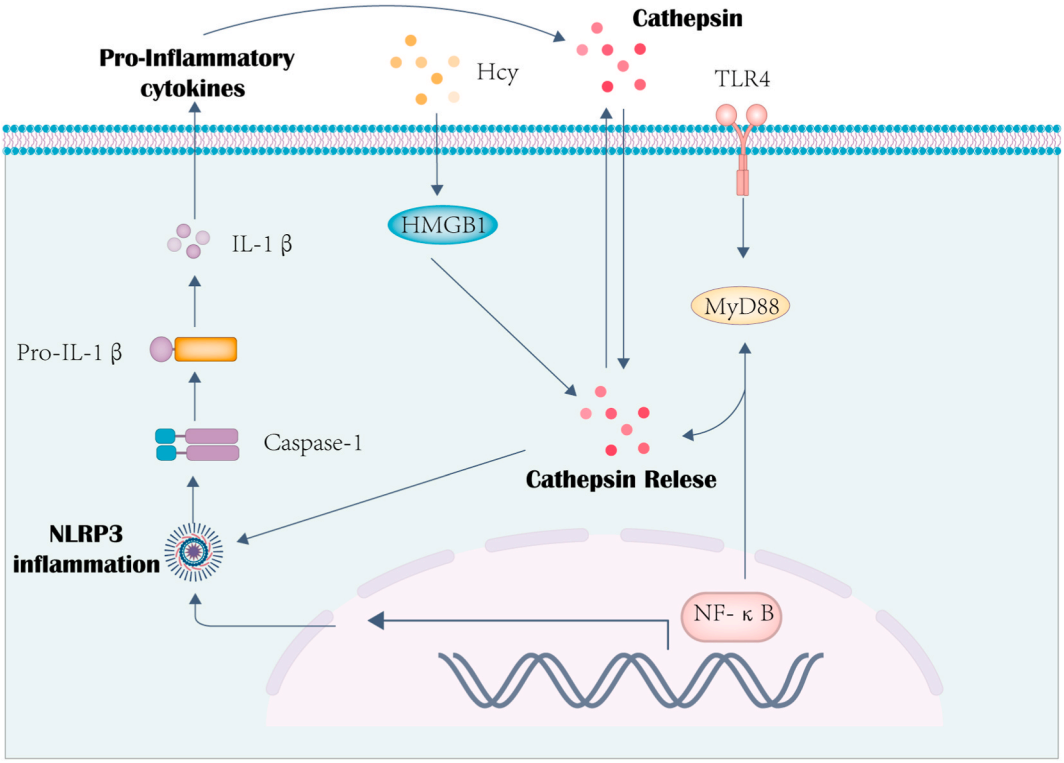

Fig. 4. Cats influence the inflammatory process associated with restenosis. Extracellular Hcy stimulates HMGB1 to promote the release of Cats, which promote the formation of NLRP3 inflammation, boost the synthesis of Caspase-1 molecules, facilitate the release of IL-1β, and influence the inflammatory process. Additionally, the Toll-like receptors pathway influences MyD88, promotes the release of Cats or the synthesis of NLRP3 inflammation, and enhances the release of proinflammatory cytokines.

disrupting autophagy, and decreasing mitochondrial function [57]. Prior research has shown that tissue damage triggers oxidative stress by generating reactive oxygen species via NADPH [58]. In our experimental mouse model of stress-related neointimal hyperplasia nduced by closure of the carotid artery, we observed that CatK and CatS deficiency suppressed the activity of NADPH, resulting in a decrease in oxidative stress and hyperplasia [59,60].

2.2.2. Cat and inflammation-related research

The role of Cats in vascular remodeling is determined by inflammation. The early contribution of cats to inflammation is mostly attributed to monocyte chemotherapy and thrombosis, as previously mentioned. In this section, we explore the correlation between Cat and inflammation, with detailed information on the underlying process depicted in Fig. 4.

Cats are intricately associated with the release of mediators of inflammation throughout the intermediate and late phases, sometimes referred to as the chronic inflammatory response. Cats stimulate endothelial cells to express adhesion molecules, namely ICAM-1/VCAM-1, leading to the recruitment of pro-inflammatory cells to the site of damage for the purpose of healing. The aforementioned cells with inflammatory properties are capable of secreting a diverse range of Cats (including CatG, S, and B) as well as other substances. Some of these substances have the potential to influence the extracellular neutral pH level, thereby impacting the body's typical vascular response to injury and leading to localized tissue damage and an accompanying inflammatory reaction in the vicinity of blood vessels.

As comprehension of diseases such as hypertension, atherosclerosis, diabetes, and obesity has grown in recent decades, their associations with chronic inflammation have been identified, and the association of Cats has likewise emerged. Prior studies have shown that the upregulation and secretion of CatS, along with vascular remodeling and accelerated atherosclerosis, may be induced by the accidental expulsion of pro-inflammatory cytokines from cells. The present data indicate that inflammatory factors are of significant importance in the expression and maintenance of Cats [61]. But can Cats accelerate the inflammatory response? Another clinical investigation suggests a causal connection between CatS and high levels of the inflammatory factors IL-6 and CRP, which are present in obese individuals, but also in certain other non-obese people regardless of sex and age [62–64]. That study demonstrated that CatS is significantly associated with inflammation in various body states, suggesting that CatS may enhance the body's inflammatory responses.

Previous research has demonstrated a link between adiposity and inflammation. Recent research findings have shown that CatD is indispensable for the functioning of ATP binding cassette transporter 1 (ABCA1), which is responsible for transporting cholesterol. Specifically, when CatD is disrupted, ABCA1 loses its ability to move, and, as a result, cholesterol builds up inside the cells [65–68]. Furthermore, it has been shown that CatB and L have a role in regulating the synthesis of cytokines and the expression of Niemann-Pick type C2 protein (NPC2) in macrophages. This, in turn, influences inflammation associated with macrophages and the transportation of cholesterol [69] (Interestingly, statins, in addition to playing an anti-inflammatory function in the vascular system through lipid-lowering mechanisms, also exert a unique anti-inflammatory effect by modulating the balance of macrophage M1/M2 populations [70]).

The CatL enzyme has an impact on the production and discharge of Cats and NF-κB through a TLR4/MyD88 signaling pathway, and it plays a role in the development of intimal hyperplasia subsequent to vascular injury [71]. The secretion of inflammatory variables in homocysteine-induced vascular inflammation is mediated by the involvement of high mobility group box-1 protein (HMGB1) and CatV. This is achieved by the upregulation of NLRP3 inflammasome and the induction of pyroptosis [72]. On the basis of those findings, researchers have developed Cat- and αvβ3 integrin-based near-infrared fluorescence biomarkers, which can be used for longitudinal detection of atherosclerosis [27]. In the future, it is anticipated that this noninvasive technology will be utilized for the early diagnosis of atherosclerosis. In addition to the close relationship between Cats and inflammation, one study utilized probes for Cat activity to quantify plaque tissue and macrophage subtypes, thereby providing a useful guide for clinical intervention [21]. In animal experiments, the use of a protease photosensitive quenching activity probe (PS-qABP) to determine inflammatory atherosclerotic areas of rapid accumulation allowed the targeted use of phototherapy to reduce the content of diseased immune cells, without affecting the content of SMCs and collagen, and ultimately reduced vascular inflammation, thereby slowing the progression of atherosclerosis. This research is expected to enhance the treatment of atherosclerosis in clinical settings [73].

2.2.3. Study on immune activity related to cats and vascular injury

There are currently few studies examining the immune-system dimension of the association between Cats and vascular injury, and no exact mechanisms are known. However, the available evidence indicates that the connection between Cats and immunity is typically mediated by vascular inflammation. CatS has the ability to play a significant role in the antigen delivery mechanism of major histocompatibility complex II (MHC II) in dendritic cells (DCs) by the elimination of p22 and p10 invariant chain (Ii) fragments [74]. In recent years, it has been demonstrated that Cats and other members of the Cat family (CatS, B, L, K, D, G, and H) are closely associated with antigen transmission in early phases of immunization [75–82]. Together, these studies provide evidence that the Cat family has a notable impact on antigen delivery. Furthermore, additional research suggests that Cats also have major involvement in the activation of lymphocytes. The deletion of the CatD gene in an animal model led to a notable decrease in the population of CD4 and CD8 cells, suggesting that this gene plays a pivotal role for the activation of immune system cells [83]. In the context of atopic dermatitis, CatE has been observed to decrease the CD4/CD8 ratio and the subsequent release of cytokines [84]. Animal studies using the CatS antagonist RO5461111 have confirmed that CatS plays an etiological role in systemic lupus erythematosus (SLE). This role involves the facilitation of MHC class II-mediated priming of T and B cells, development of germinal centers, and maturation of B cells into plasma cells [85]. Numerous studies have demonstrated that Cats are involved in antigen delivery and lymphocyte activation; however, few studies have been conducted in the context of atheromatous plaques or vascular injury, leaving great potential for new and important

discoveries.

2.3. Function and performance of cats in the terminal phase of post-stent restenosis

2.3.1. Cats are involved in the remodeling of the extracellular matrix after vascular injury

In recent years, Cats have been suggested to possess the ability to sustain their physiological functions under neutral or mildly alkaline environments, namely those situated beyond cellular boundaries. Moreover, Cats have been observed to engage in a diverse range of biologically significant activities that are morphologically associated, including but not limited to extracellular matrix remodeling and angiogenesis. Cats have also been observed to facilitate the restructuring of blood vessels and various human organs, including adipose tissue, the heart, liver, and other organs. This process primarily involves the degradation of the extracellular matrix, specifically elastin and collagen, followed by stimulation of the synthesis of substitute substances. Such remodeling is frequently observed in the context of cardiovascular disorders such as coronary artery disease myocardial infarction, cardiac failure, and abdominal aortic aneurysm, and is crucial for the maintenance of organ functionality.

CatA has been shown to be involved in ventricular restructuring and ventricular cardiomyopathy in rodents after myocardial ischemia/reperfusion. One potential mechanism by which CatA contributes to these ventricular effects in experimental mice is through the degradation of extracellular oxide dismutase [86,87]. CatG demonstrates strong chemoattractant and inflammatory mediator properties inside the non-stressed or wounded cardiac tissue by digesting and activating cytokines belonging to the IL-1 family. These actions lead to adverse cardiac remodeling and impaired cardiac function. Therefore, the strategic targeting of Cats may be a promising therapeutic approach in mitigating coronary artery disease and promoting cardiac remodeling and function in the aftermath of injury or stress.

Cats are involved in extracellular matrix remodeling, but it has not been systematically determined whether distinct tissue proteins play different functions in various diseases or have different effects on clinical outcomes. CatL, but not CatK or CatV, has a considerable impact on abdominal aortic aneurysms, according to a study examining the association between Cats and abdominal aortic aneurysm. Prior research has predominantly focused on examining the effects of inflammatory mediators, namely IL-1β and TNF-κB, on Cats participants. However, it is evident that the degree of response exhibited by Cats towards inflammatory stimuli exhibits considerable variation among Cat family. Several experimental studies have found, for instance, that the regulation of inflammatory factors is not always effective in clinical practice and have suggested that there are unique regulatory mechanisms for Cats. Recent research has revealed that Cats are regulated by microRNA epigenetic expression and that their upregulation contributes to the instability of atherosclerotic plaques.

2.3.2. Study of cats in SMCs

The expeditious advancement of sequencing of single cells and cellular-lineage tracing methodologies has facilitated the identification of diverse VSMC phenotypes in the context of vascular ageing, atherosclerosis (AS), abdominal aortic aneurysm (AAA), and other pathological conditions. Recent findings have shown that Cats play a role in the phenotypic alteration of vascular smooth muscle, and thereby contribute to the processes of repairing vascular injuries and developing intimal hyperplasia. In the field of animal studies, it has been observed that CatD and ACE have a role in facilitating the expression of Ang II. Consequently, this expression of Ang II contributes to the conversion of VSMCs from a contractile phenotype to a synthetic phenotype in rodents. As a result, this process significantly impacts the advancement of hypertension [88,89]. Numerous experimental studies conducted in vivo and in vitro have provided evidence that H_2S can upregulate elastin levels by inhibiting Stat3/CatS signaling, and can prevent elastin loss and degradation, thereby stabilizing HASMCs as contractile VSMCs (Marker: SM α-actin and SM22α) and decreasing vascular calcification [90,91].

KLf4, a highly expressed marker in synthetic VSMCs, has been shown to be associated with members of the Cat family (CatL, C and K) [92–94]. While there is existing evidence showcasing the involvement of KLF4 in atherosclerosis, vascular ageing, and restenosis, there is a limited body of research exploring the specific mechanisms by which Cat and KLF4 operate in these areas. In 1997, researchers made a significant finding on the cellular composition of atherosclerotic plaques in the human aorta. Specifically, they observed that cells expressing both CD68 and α-SMA were mostly localized in regions of these plaques that exhibited a high lipid content. Prior to the utilization of cellular lineage tracing, the aforementioned research had limitations in determining whether the chimeric cells originated from VSMCs that expressed monocyte markers, macrophages that expressed VSMCs markers, or neither. The process of phagocytosis in the context of atherosclerosis relies on the macrophage-like characteristics of VSMCs. The conversion of VSMCs to macrophage-like VSMCs is primarily influenced by elevated levels of oxidized low-density lipoprotein (oxLDL) and cholesterol, which are the most significant metabolic variables in this transformation. Numerous studies have shown that the expression and activity of Cats (CatS, L, K, D and B) are stimulated by oxLDL or cholesterol [93,95–103]. There have also been reports of a negative correlation between CatS and HDL-C in patients with abdominal aortic aneurysm [102]. CatD is involved in droplets of facilitated lipolysis, and autophagy reduces oxLDL accumulation in cells [97,104]. Furthermore, it has been observed that the novel anti-atherosclerotic factor known as sirtuin1 (SIRT1) has the ability to stimulate autophagy in cardiac myocytes through the autophagy-lysosomal pathway [105].

The functional equivalence between mesenchymal-like vascular smooth muscle cells (VSMCs) and synthetic VSMCs is evident, as both cell types exhibit a notable proliferation capacity and possess the capability to undergo phenotypic transformation into different VSMC phenotypes, thereby facilitating the process of vascular healing in response to damage. During artery injury, the activation of KLF4 has been shown to result in an upregulation of mesenchymal markers, including stem cell anti-1 (SCA1)/LY6A, CD34, and CD44, while causing a downregulation of contractile proteins in VSMCs [106]. Current Cat research in this area concentrates primarily on

acute promyelocytic leukemia and bone marrow microenvironment [107,108]. However, no pertinent research exists on Cat and mesenchymal-like VSMCs.

Lumican (LUM), biglycan (BGN), and decorin (DCN) are recognized as unique markers for fibroblast-like VSMCs. Furthermore, fibroblast-like VSMCs exhibit three distinct roles, namely ECM formation, stimulation of cell-matrix adhesion, and facilitation of cell proliferation. They have a pivotal role in the pathogenesis of arterial stiffness, atherosclerosis, and various other pathological conditions [109,110]. According to contemporary research, there is an occurrence of cholesterol-mediated conversion of VSMCs into fibroblast-like VSMCs, which has been implicated in the development of atherosclerosis [111–113]. Cats, specifically CatB, D, L, S, and K, have been shown to play a crucial role in the metabolism of cholesterol [107,111–114].

Vascular calcification represents a fundamental characteristic of atherosclerosis, a condition that is commonly observed in the older population and individuals diagnosed with chronic kidney disease (CKD) [115]. Prior studies have suggested that the activation of osteogenic genes plays a significant role in the process of vascular calcification. However, newer studies have provided evidence indicating that the transition of VSMCs into an osteogenic phenotype is the principal underlying factor contributing to vascular calcification [116–118]. Cats, namely cathepsins K and V, play a significant role in the process of arterial calcification, which contributes to the pathogenesis of various disorders including CKD, osteoarthritis, and cardiovascular disease (CVD) [119–122]. But whether Cats directly affect the transformation of VSMCs into osteogenic VSMCs is still unknown.

3. Conclusion

Cathepsins play essential roles in restenosis, as they primarily affect vascular endothelial cells and are associated with such processes as thrombosis, inflammation, immunity, and VSMC phenotypic transformation. The most recent Cat-based tool using fluorescent probes can actually detect the level of inflammation in atherosclerosis and the type of macrophages in the lesion and direct site-specific treatment by spectroscopy. Inhibition of specific Cats can reduce thrombosis, the release of inflammatory factors, extracellular matrix remodeling, VSMC proliferation and migration, and VSMC phenotype conversion. Thus, Cats are crucial both in the development of restenosis and its treatment and prevention. Although the current research regarding Cats in restenosis has made important breakthroughs, and relevant detection methods and treatment programs are gradually being developed, the specific mechanisms of Cats in restenosis immunity and VSMC phenotype transformation are still in the exploratory phase. In addition, there has been a new understanding of the recent studies and endothelialization of coated stents [123,124]. Further investigation is necessary to establish a theoretical framework for a Cat-oriented approach to addressing re-endothelialization, thrombosis, and restenosis following stenting and/or atherectomy procedures.

Data availability statement

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Hai Long Wang: Writing – original draft, Conceptualization. **Megumi Narisawa:** Data curation, Formal analysis. **Pan Wu:** Writing – review & editing, Data curation, Formal analysis. **Xiangkun Meng:** Writing – review & editing, Data curation, Funding acquisition. **Xian Wu Cheng:** Writing – review & editing, Funding acquisition, Conceptualization, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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