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Review article

Platelet-inspired targeting delivery for coronary heart disease

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ABSTRACT

Platelets play a pivotal role in many physiological and pathological processes, with their special targeting/adhering properties towards infarcted myocardium, injured or dysfunctional endothelium, and growing thrombus. Leveraging the site-targeting/adhering property, a variety of platelet-inspired targeting delivery (PITD) designs have been developed, the majority of which are reached by hitchhiking live platelets, cloaking nanoparticles with platelet membranes and mimicking platelet functions. With PITD, drugs or regenerative cells can directly reach targeted sites with minimized systematical distribution thus being of great clinical benefits. Coronary heart disease (CHD) is a major health burden worldwide. Plenty of PITD designs have shown promising outcomes for the treatment of CHD in preclinical models, especially in thrombolysis and post-percutaneous coronary intervention (post-PCI) anti-restenosis. Besides, PITD applications in cardiac protection and atherosclerotic plaque imaging are also under investigation. What's more, the potential benefits of PITD in the field of cell-based therapy are also attracting growing attention since it may resolve the problem of low arriving and retention efficiency, which are also particularly discussed in this review. In brief, our focus is putting on PITD strategies designed for the treatment of CHD, which hopefully can facilitate further optimization of this direction.

1. Introduction

Coronary heart disease (CHD) is a leading cause of morbidities and mortalities on a global scale [1]. Myocardial ischemia and necrosis are followed by ventricular remodeling, dilatation, and heart failure owing to the poor regenerative potential of adult cardiomyocytes [2]. Though the rapid advancement in pharmacological and interventional therapeutics has resulted in a significant decrease in mortality, practical treatment efficiency is still of unmet clinical need. In terms of traditional revascularization treatments, percutaneous coronary intervention (PCI), the most widely applied coronary vascular recanalization strategy, can save hypoxic cardiomyocytes, preserve cardiac function and lead to a better prognosis for selected patients [3]. Though the rapid progress in the procedures [4], stents [5], and intracoronary imaging [6,7], PCI is not totally free from stent-related complications [8] such as in-stent restenosis and thrombosis. Intravenous thrombolysis is another important revascularization approach for patients presenting with ST-segment elevation myocardial infarction (STEMI). However, systemic bleeding complications are also an important issue of clinical concern. Above mentioned problems partially originate from the low delivery efficiency of drug administration at the targeted lesions,

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Table 1
Studies of PITD for CHD therapy in animal models.

Strategy	Cell/Cargo	Animal model	Delivery	Quantification of targeting/Retention	Functional improvement	Refs.
Cell-based therapy						
Platelet hitchhiking	Allogeneic PBMCs	Mouse	i.v.	Significant accumulation in heart 3 h post I/R injury No accumulation 24 h post I/R injury	↑Cardiac function ↓Fibrosis ↑Capillary density ↓Inflammatory response	[31]
	Allogeneic iVPCs	Mouse	i.v.	Serious pulmonary entrapment	↑Cardiac function ↓Fibrosis and infarct size ↑Neovascularization	[32]
	Endogenous EPCs	Mouse	i.v.	Enhanced accumulation in the MI area	↑Cardiac function ↓Fibrosis ↑Neovascularization ↑Cardiomyocytes proliferation	[36]
	Endogenous EPCs	Mouse	i.v.	Increased accumulation in the MI area	↑Cardiac function ↓Infarct size ↑Neovascularization ↑Cardiomyocytes proliferation	[37]
Membrane fusing	CSCs	Rat and porcine	i.c.	Boosted retention in heart 24 h post-injection Very little persistence 4 weeks post-injection	↑Cardiac function ↓Infarct size	[38]
Membrane cloaking	Paracrine factors of CSCs	Mouse Rat	i.v. i.v.	14.9-fold higher concentrations in the infarcted area compared with bare nanocells	↑Cardiac function ↑Neovascularization	[45] [46]
	Carvedilol MSC-derived EVs	Mouse	i.v.	3.4- and 8.6-fold higher concentrations in the heart than in the liver and kidney respectively Increased accumulation in I/R regions Increased circulation time than EVs Increased targeting ability to monocytes/macrophages/injured endothelial cells	↑Cardiomyocytes proliferation ↑Activation of endogenous stem/progenitor cells ↓Heart remodeling ↑Cardiac function ↓Myocardial cell apoptosis ↑Cardiac function ↓Inflammatory response ↑Cardiac function ↓Heart remodeling ↑Neovascularization	[49, 51]
	Resolvin D1	Mouse	i.v.	Increased accumulation in the MI area	↑Neovascularization	[50]
	Circulating EVs	Mouse	i.v.	Increased retention in I/R heart 24h post-injection	↑Cardiac function ↓Heart remodeling ↓Fibrosis ↑Neovascularization ↑Cardiac function ↓Heart remodeling ↓Infarct size	[52]
Platelet mimicking	DOPC	Mouse	i.v.	Increased targeting ability to monocytes but not endothelial cells Increased accumulation in the infarcted heart	↑Cardiac function ↓Inflammatory response	[54]
	miR-21 mimics	Mouse	i.v.	Increased targeting ability to monocytes/macrophages Increased accumulation in the heart	↓Inflammatory response ↓Fibrosis ↑Neovascularization ↑Cardiac function	[55]
Thrombolytic therapy						
Platelet mimicking	SK	Mouse	i.v.	Increased localization in the thrombosed carotid Enhanced binding to thrombus -associated active platelets	↓The time of vessel occlusion ↓Bleeding time	[61]
	uPA			Increased targeting to activated platelets	↑Thrombolysis	[62]

(*continued on next page*)

Table 1 (*continued*)

Strategy	Cell/Cargo	Animal model	Delivery	Quantification of targeting/Retention	Functional improvement	Refs.
	tPA	Mouse	i.v.	Increased accumulation in the regions of clot formation 25-fold accumulation at regions of vascular occlusion	↓The time of vessel occlusion ↑The safety of thrombolytic therapy ↑Clot-lysing ↓Unwanted bleeding and neurotoxicity	[65]
	r-tPA	Rabbit	i.a.		↑The rate of recanalization	[65, 66]
Membrane cloaking	tPA	Rat and Mouse	i.v.	Increased adhesion to damaged endothelial cells Increased accumulation at the site of the target thrombus	↑Mitochondrial respiratory chain function ↑Thrombolytic activity ↑Capillary angiogenesis ↓Infarct size ↓fibrosis ↓Inflammatory response	[70]
Anti-restenotic therapy						
Platelet mimicking	DEX	Rat		Increased adhesion and uptake in HAECs and higher retention	↓Restenosis	[82]
Membrane cloaking	JQ1	Rat	i.v.	Increased homing capacity to the balloon-injured carotid artery wall	↑Re-endothelialization ↓Development of neointima	[88]
	IL-10	Rat	i.v.	No significance in the binding ability to macrophages Increased accumulation at the site of vascular injury	↓Proliferation of SMCs and ECs ↓Phenotypic transformation of SMCs ↓Neointima area	[89]
Atherosclerosis imaging						
Membrane cloaking	MRI contrast agent	Mouse	i.v.	Increased binding ability to foam cells and activated ECs Increased targeting ability	↑Observation at the site of atherosclerotic plaque at different stages of development	[91]

Abbreviations: PBMCs, peripheral blood mononuclear cells; iVPCs, induced vascular progenitor cells; EPCs, endothelial progenitor cells; CSCs, cardiac stem cells; EVs, extracellular vesicles; MSC, mesenchymal stem cell; i.v., intravenous; i.c., intracoronary; i.a., intraarterial; DOPC, 1,2-dioleoyl-sn-glycero-3-phosphocholine; I/R, ischemia-reperfusion; MI, myocardial infarction; uPA, urokinase plasminogen activator; SK, streptokinase; tPA, tissue plasminogen activator; UK, urokinase; DEX, dexamethasone; HAEC, human aortic endothelial cells; SMCs, smooth muscle cells; ECs, endothelial cells; MRI, magnetic resonance imaging.

thus being accompanied by low local concentrations of delivered drugs and undesirable systemic side effects [9]. Therefore the precise targeted drug delivery approaches which can optimize drug distribution in long peripheral circulation are necessary and valuable in clinical practice.

The concept of targeting drug delivery was originally developed for cancer treatment [10] and soon applied in other clinical fields for its great practical potential [11]. Ideally, with targeted delivery platforms, intravenously administered drugs can precisely exert their effects only at the targeted sites, so off-target distribution and blood clearance can be thus minimized. Nevertheless, it is difficult to find a wonderful strategy with sophisticated in vivo targeting ability and excellent biocompatibility to realize efficient targeted drug delivery for CHD. Platelets, known as circulating blood cells, play an essential role in several pathological progress of CHD including thrombosis, inflammation, and cardiac regeneration [12], inspiring researchers to come up with many targeted delivery systems. As sensitive sentinels of vessel integrity, these small, anucleate disc-shaped cells [13] can promptly target and adhere to injured vessels and progressing thrombi, which is mainly mediated by surface molecules such as GPIb-V-IX, GPVI, and GPIIb/IIIa [14]. Compared with other targeting strategies, platelet-inspired targeting delivery (PITD) presents advantages of both general cell-based delivery such as excellent biodegradability and immunocompatibility, and its unique characteristics including natural site-specific targeting and appropriate half-life [15]. Therefore, platelets, platelet-mimics, and their membrane derivatives have undergone intensive investigations and yielded great potential for targeted realization of the treatment for CHD with the help of rapidly developing biotechnology **(Table 1)**.

This review focuses on the application of PITD in cell-based therapy, thrombolysis, and anti-restenosis after stent implantation. PITD has shown great potential in cardiac regeneration with stem cells that can be viewed as special drugs via increasing the rates of homing and retention of transplanted cells [16]. With PITD, targeting delivered thrombolytic drugs can revascularize culprit arteries with seldom hemorrhages [17]. In addition, anti-restenosis drugs with PITD can attenuate this common post-PCI complication without another invasive procedure, while these drugs are given invasively by eluted in stents or coated on balloons in the current clinical practice. Besides, PITD also attracts increasing attention for atherosclerotic plaque imaging (Fig. 1).

1.1. PITD for cell-based therapy

Cell-based therapy with implanting autologous or allogeneic stem cells is paying growing attention to its potential contribution towards cardiac repair and regeneration [18]. Among this inflammation plays an important role in post-MI cardiac repair and remodeling and the monocyte/macrophage is the focus of the process [19]. In theory, implanted cells can improve cardiac function through directly replenishing the lost cardiomyocytes and/or exerting indirect impacts including paracrine effects [20] and immune-stimulatory effects [21]. However, the low rates of homing and retention of implanted cells into the targeted sites in vivo are the most important reasons for being incapable of translation in clinical practice during a recent couple of decades [22]. Only less than 10% of implanted cells remain alive in the heart regardless of the delivery routes 24h after administration [23,24], since they are

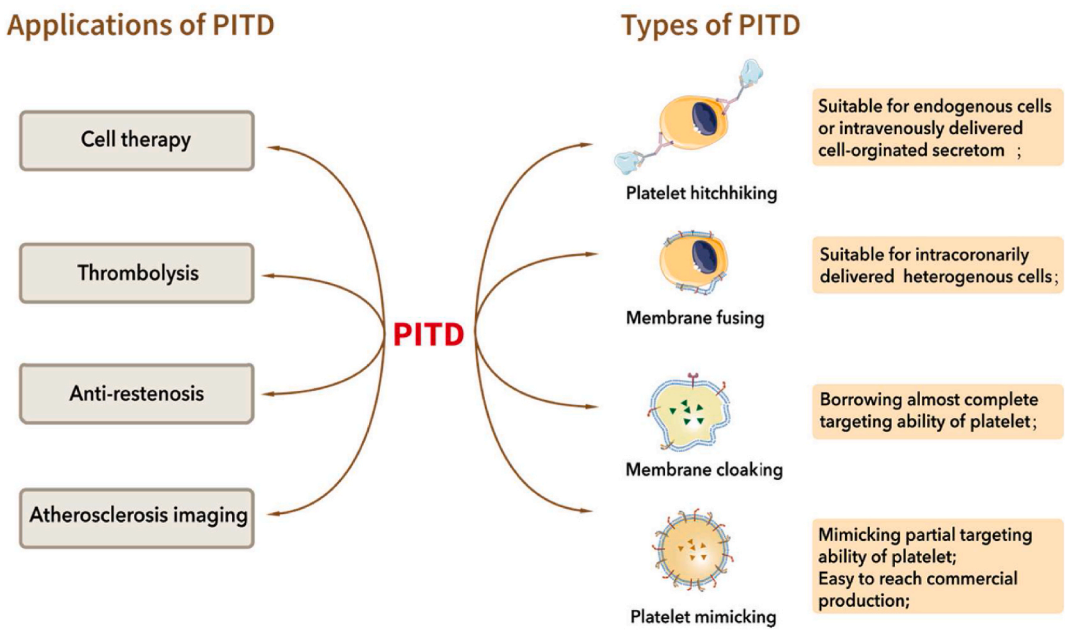

Fig. 1. Major designs and applications of platelet-inspired targeting delivery (PITD) for coronary heart disease (CHD)
The applications of PITD for the treatment of CHD concentrate on cell-based therapy, thrombolysis, anti-restenosis, and atherosclerosis imaging. In general, PITD could be divided into four types [1]: platelet hitchhiking [2]; membrane fusing [3]; membrane cloaking [4]; platelet mimicking. Their main features are briefly outlined.

usually spilled over quickly from the myocardium and washed out by the bloodstream [25]. Therefore, the targeting delivery of implanted cells might be the promising method to improve retention, regulate myocardial inflammation, and ultimately enhance therapeutic efficacy. PITD could be a promising approach to facilitating intravenous delivery and the increased retention of infused cells in the heart. Besides, quiescent platelets are recruited and activated by strong agonists such as damaged endothelium, exposed sub-endothelial tissue, and non-physiological shear flow conditions [26,27]. Platelets also play a part in the mobilization of autologous progenitor/stem cells [28] by augmenting their targeting and adhesive properties after they are released from the bone marrow in response to myocardial infarction (MI) [29]. Above all, these properties enable platelets and their derivatives to be ideal performers for targeting the delivery of cells in the treatment for CHD.

1.1.1. Applications of platelet hitchhiking

Different from small-molecule drugs, donor cells are big in size, therefore it is practicable to take advantage of live platelets such as platelet hitchhiking with the support of various synthetic antibodies including bispecific, biorthogonal and direct membrane-decorating antibodies.

1.1.1.1. With bispecific antibody. The construction of bispecific antibodies involves connecting two different recognition domains on the antibody molecule, which can be different antibody fragments, such as Fab, Fc, and scFv. As a type of synthetic antibody, bispecific antibodies can spontaneously bind to two receptors with the same affinity [30]. For example, by pre-incubating peripheral blood mononuclear cells (PBMCs) and Tand-scFv$_{\text{Sca-1+GPIIb/IIIa}}$, this antibody can link PBMCs to circulating platelets for the PITD by its two tandemly linked scFvs which respectively link to stem cell antigen-1 (Sca-1) receptor abundant on PBMCs and GPIIb/IIIa receptor highly expressed on activated platelets. With Tand-scFv$_{\text{Sca-1+GPIIb/III}}$, PBMCs can hitchhike platelets and thus be directly brought to the ischemic myocardium. The targeted-PBMCs are remarkably accumulated in the myocardium and lead to a more significant increase in left ventricular ejection fraction (LVEF) and neovascularization, and a reduction in cardiac fibrosis and inflammatory reactions than those in the untargeted-PBMCs group after 4 weeks [31]. Tand-scFv$_{\text{Sca-1+GPIIb/IIIa}}$ is also tested in induced vascular progenitor cells (iVPCs) with abundant Sca-1 [32]. iVPCs belong to partly reprogrammed induced pluripotent stem cells (iPSCs) which have the definite developmental potential for revascularization and stimulate the growth of coronary collaterals [33]. Though trapped by the pulmonary microvasculature, intravenously injected targeted-iVPCs reduce infarct size, and fibrosis, enhance vessel density and restore cardiac function. Moreover, Pennapa et al. [34] develop new polymeric nanoparticles prepared from poly lactic-co-glycolic acid (PLGA), which are designed to be coated with GPIbα, the binding site of a platelet receptor complex to von Willebrand factor (vWF) and CD34, a surface marker of endothelial progenitor cells (EPCs), respectively. The Tand-scFv$_{\text{CD34+GPIbα}}$ nanoparticles can capture EPCs to the endothelial injured site to repair the injured vascular wall and simultaneously accelerate endothelium regeneration.

1.1.1.2. With bioorthogonal antibody. Another way to achieve platelet hitchhiking is the bioorthogonal click reaction, an extremely selective and biocompatible chemical reaction that can bind two different antibodies together [35]. Taking advantage of pretargeting and bioorthogonal chemistry, Li et al. [36] constructed a pretargeting and bioorthogonal chemistry (PTBC) system for PITD aiming to facilitate the natural mobilization of autologous EPCs in response to MI. In the PTBC system, CD34 antibodies (targeting of EPCs) and CD41 antibodies (targeting of platelets) are first modified using bioorthogonal azide (Az) and dibenzocyclooctyne (DBCO) attached polyethylene glycol (PEG) derivative, respectively. After injecting DBCO polymer (DBCO-PEG-CD41) to pretarget circulating platelets and with the help of the natural infarct-targeting effect of platelets, these antibodies concentrate at the infarcted area via platelet hitchhiking. After 48h of pretargeting interval, azide-modified CD34 (Az-PEG-CD34) is then given and binds to EPCs. Then Az groups on the EPCs recognize and react with DBCO groups on platelets via bioorthogonal click reaction. As EPCs are engaged with platelets and accumulate in the infarcted area for cardiac repair, promoted angiogenesis, improved cardiac functions, and decreased fibrosis are observed in the MI mice after four weeks. This two-step capturing strategy can minimize the potential possibility of thrombosis because cells and platelets are linked together in the targeted area instead of the vessels.

1.1.1.3. With direct membrane-decorating antibody. Another PITD for cell therapy is also associated with antibodies and CD34^{+} EPCs, in which the CD34 antibodies are directly decorated on the platelet surface [37]. CD34-armed platelets (P-CD34) can effectively capture circulating CD34^{+}EPCs and guide them to the injured cardiac regions without causing thrombosis or any cytotoxicity. With capture efficiency at about 33.6%, intravenously injected P-CD34 significantly increases EPC concentrations in infarcted areas and leads to substantial neovascularization and improvement of cardiac function after 4 weeks in MI mice.

1.1.2. Applications of membrane fusing

Though none of the above-mentioned animal experiments show increased thrombosis, applying complete and live platelets is potentially the risk of promoting coagulation through intracellular machinery. This problem can be solved by applying pure platelet membranes. Since giving up cytoplasmic proteins can eliminate intracellular reaction crusade which may activate uncontrollable coagulation, and the infarct-targeting ability of platelets that largely relies on surface glycoproteins is almost unaffected.

Being inspired by this strategy, Tang et al. [38] created the platelet-nanovesicle-fused cardiac stem cells (PNV–CSCs) by decorating the surface of CSCs with PNVs through membrane fusion. PNVs are small particles derived from platelets which carry all of platelet membrane glycoproteins. Therefore, PNV-CSCs possess the infarct-targeting ability from platelets and the whole efficacy of CSCs. In animal studies, PNV-CSCs exhibit superior retention and engraftment propensities, correspondingly resulting in improved cardiac

function and reduced infarct size compared with undecorated CSCs. Considering the size of CSCs [39] and the necessity of avoiding entrapment in pulmonary circulation, PNV-CSCs are suitable for intracoronary injection which is more acceptable in clinical practice.

Compared with platelet hitchhiking, PITD based on membrane fusing technology is fast, straightforward, and non-platelet-like aggregation. However, cell-based therapy is always in debate since the so-called CSCs are now widely regarded to be heterogeneous and unable to directly differentiate into cardiomyocytes [40]. Actually, though the animal studies of CSCs show a reproducible improvement in cardiac function of the ischemic heart, several indirect effects such as paracrine behaviors [41], endothelial differentiation [40], and acute inflammatory responses [42] can partly explain the benefits. In general, this PITD strategy is practically applicable, and relevant studies related to other donor cells with definite differentiation potential should be carried on in the future.

1.1.3. Applications of membrane cloaking

The technology of membrane cloaking is also utilized in PITD during cell-based therapy. But the cargo delivered is not cells per se, but cell-secreted factors. As above mentioned, the paracrine effect is one of the prevalent explanations for the benefits related to adult human cell-based therapy [20]. For example, paracrine factors generated by CSCs showed similar therapeutic benefits compared with CSC implantations [43]. Besides, adult human cells secrete a wide variety of paracrine factors after transplantation, which can promote cardiac repair by influencing adjacent host cells in spatial manners [44]. Compared with whole cell transplantation, the "cell-free" strategy, which means purely leveraging secreted factors instead of seeking direct transdifferentiation, emerges as a new direction and is more suitable for intravenous injection.

Given the obstacle of low homing rate, the platelet-inspired nanocells (PINCs), collaborating platelet membrane with a core of paracrine factors from cardiac stromal cells (a type of adult human cells), is a potential PITD strategy for "cell-free" strategy to efficiently target to infarcted heart and exert therapeutic effects [45]. Systematically administered PINCs are shown with higher concentrations in the infarcted heart than in the liver or kidney, thus resulting in improved cardiac function and mitigated ventricular remodeling in the mice with ischemia-reperfusion (I/R) injury. Besides, Zhou et al. [46] also demonstrate the targeting ischemic-damaged myocardial tissue ability and the protective postinjury cardiac function of platelet-membrane-encapsulated Carvedilol. Extracellular vesicles are considered to be intercellular communication carriers [47]. Moreover, the role of extracellular vesicles as conveyors in immune responses has already been demonstrated [48]. Extracellular vesicles based on PITD can provide new ideas for immune regulation therapies for CHD. In the mouse model of myocardial I/R injury, the intravenously injected platelet membrane-modified extracellular vesicles (P-EVs) based on the membrane fusion method mainly bind with circulating monocytes into the ischemic myocardium and released the functional miRNAs, which regulate immune microenvironment to realize cardiac repair by polarizing the inflammatory macrophages (M1 phenotype) to reparative macrophages (M2 phenotype) [49]. Besides, Weng et al. [50] developed a platelet-targeted delivery platform by hybridizing the platelet membrane with liposomes. The release of anti-inflammatory Resolvin D1 in LPs promotes the transformation of macrophage phenotype and clearance of dead cells, effectively preserving cardiac function in myocardial I/R-induced mice. In addition to facilitating anti-inflammation effects, the P-EVs delivery system can enhance the angiogenesis potency to protect against acute myocardial injury and cardiac remodeling after I/R [51,52]. In general, the application of membrane cloaking brings about a novel therapeutic option for CHD patients and deserves further study.

1.1.4. Applications of platelet mimics

Platelet mimics refer to synthetic particles mimicking the appearance, physiochemical properties, and/or functions of live platelets, which are related to a wide variety of biotechnological designs.

On the way from the spleen to the infarcted heart, the recruited monocytes are reported to interact with circulating platelets [53]. Cheng et al. [54] mimic the monocyte-platelet interaction by creating platelet-like proteoliposomes (PLPs) which carry whole platelet membrane proteins of the surface. When being systematically injected, PLPs hitchhike circulating monocytes which act as a "shuttle bus" and target to infarcted heart. After infiltrating in the targeted areas, compared with purely injecting Cobalt protoporphyrin IX (CoPP), the PLPs are shown to enhance the therapeutic effect of CoPP, which can induce strong heme oxygenase-1 expression in the heart, thus downregulating the expression of several proinflammatory genes, and eventually improve cardiac function. Another experiment also uses platelet mimics to regulate the phenotype of macrophages to facilitate anti-inflammation effects [55]. Under the coating of PLPs, mesoporous silica nanospheres with a payload of miR-21, an anti-inflammatory agent, bind to $Ly6C^{+}$ monocytes that show chemotaxis toward the injured heart, and then be carried to the injured areas. Then miR-21 directly enters the cytoplasm of monocytes to realize the reparative reprogramming of the inflamed macrophages derived from it. In vivo, administration of the resulting formula can effectively preserve the cardiac function of mice undergoing myocardial I/R. The prominent advantage is that platelet biomimetic technology organically mimics the targeting property of the platelet membrane. Besides, the minimal invasiveness and biological safety also make this nano-platform a promising approach to cell-based therapy.

1.2. PITD for thrombolytic therapy

Despite the primary PCI being the predominant revascularization strategy for patients with STEMI, thrombolysis remains an important strategy, especially in those districts with poor healthcare provisions. The Regular thrombolytic drugs are plasminogen activators (PAs), including urokinase plasminogen activator (uPA), streptokinase (SK), and tissue plasminogen activator (tPA) [56]. However, the utilization of thrombolysis is limited by the narrow therapeutic time window and hemorrhagic complications. These obstacles are derived from undesirable off-target fibrinolytic actions associated with the traditional delivery of PAs [57]. In order to make PAs exert their pharmacological actions exactly at the site of thrombi, several targeted delivery strategies are under investigation [58–60], and PITD is the most promising one. In the process of thrombosis, activated platelets are recruited to the thrombus and link

with each other through interaction between surface glycoproteins. The PITD aims to use the thrombus-targeting and adhering ability of platelets in this process. Generally, PITD for thrombolytic therapy is mostly achieved by platelet-mimicking drug carriers and membrane cloaking strategy as demonstrated below.

1.2.1. Platelet mimics

The aims for targeting thrombolysis usually mimic thrombus-targeting or shear-inspired adhesion properties of platelets, with the help of accurate site-specific drug release.

1.2.1.1. Ligands/antibodies binding and enzyme-triggered releasing. Some delivery platforms use ligands or antibodies decorated nanoparticles along with an enzyme-triggered release system for thrombolysis. Pawlowski et al. [61] developed the platelet microparticle-inspired nanovesicles (PMINs) to precisely send SK to the site of thrombi. They decorate liposomal vesicles with high-selective hetero-multivalent peptide ligands which can specifically bind to both stimulated GPIIb/IIIa and P-selectin on activated platelets. The precise release of SK is triggered by phospholipase-A2 (sPLA2), a thrombus-relevant enzyme that is abundant in the atherothrombotic microenvironment in a concentration-dependent way. PMINs do not interact with circulating quiescent platelets, they are degraded when they stick to activated platelets in a sPLA2 abundant place, namely the site of thrombi. The active platelet-directed thrombus site-selective delivery and enzyme-triggered release of thrombolytic drug can render targeted fibrinolytic action and minimize off-target systemic side effects. Unlike PMINs whose binding is mediated by hetero-multivalent ligands, an active thrombolytic agent, uPA, is successfully encapsulated in the polymer carrier system that merely targets stimulated integrin GPIIb/IIIa on activated platelet surfaces. These multifunctional polymer capsules are cleavable by the serine protease thrombin to trigger the release of the thrombolytic agent uPA at the area of acute thrombosis [62].

1.2.1.2. Shear-triggered releasing. Except for ligand interactions, the platelet reactions towards high fluid shear are also mimicked. After stenosis happens, fluid shear stress will locally increase by one or two orders of magnitude [63]. This abnormal high shear stress is a strong agonist for quiescent platelets, which can activate the adhesion of platelets to the surface of adjacent narrowed vessels [64]. A biomimetic strategy called shear-activated nanotherapeutics (SA-NTs) is invented by mimicking this reaction for the treatment of acute vascular thrombotic occlusion [65]. As platelet mimics (≈4 μm), SA-NTs can stably flow in normal bloodstream but break up into individual nanoparticles (≈200 nm) and release tPA under pathological levels of shear (>100 dyne/cm2). Share-targeted delivery of tPA using SA-NTs shows an efficient clot dissolution ability in animal models with mesenteric injury, fatal pulmonary embolism, and carotid vessel occlusion [65,66]. Though thrombolysis with SA-NTs is of great practical value for partial vascular occlusive lesions, this strategy cannot replace normal interventional processes for total occlusive lesions. Under these circumstances, the guiding wire is indispensable to create an arterial flow channel inside thrombi, while SA-NTs cannot release without high shear stress.

1.2.2. Platelet membrane cloaking

Inspired by an “all-in-one” drug delivery platform to treat multiple myeloma and its common complications of vascular obstruction by leveraging platelet membrane [67,68], a platelet membrane-cloaked argatroban-loaded polymeric nanoparticle (PNP_{Arg}) is developed for thrombus therapy. The PNP_{Arg} can rapidly and preferentially target the thrombosed vessels and remarkably suppress thrombus formation and the levels of inflammatory cytokines [69]. Guo et al. [70] constructed a thrombus-targeting and responsive biomimetic nanoparticle (PTPN) to treat MI sequentially spatially and temporally. PTPN, loaded with thrombolytic effect tPA, targets the thrombus due to the thrombus homing property of the surface-coated platelet membrane and disintegrates in response to slightly acid conditions, thereby releasing tPA to re-open the infarcted arteries. Besides, Liu et al. [71] designed a platelet membrane-cloaked nanotube biomimetic delivery system with enhanced thrombolytic efficiency. Nanotubes (NTs) have an excellent clot-penetration property, loading a protein thrombolytic drug urokinase (UK) and grafting platelet-targeting arginine glycine-aspartic peptide (RGD) on the surface. After the platelet membrane cloaking on NT-RGD/UK, the NTs can target delivery UK and penetrate deeply into the thrombus clots to recanalize blood vessels. In general, the platelet membrane-cloaked nanoparticle delivery strategy provides a promising platform for targeted drug delivery to eliminate the emergence of thrombi and minimize their side effects.

1.3. PITD for anti-restenotic therapy

Stent implantations are widely used to completely restore the lumen diameter of stenotic or obstructive coronary arteries for CHD patients. However, arterial damage following stent implantations may lead to neointimal hyperplasia and vascular smooth muscle cell proliferation, even result in in-stent restenosis (ISR), a common cause of the second interventional operation for post-PCI [72,73]. ISR means a reduction in lumen diameter inside stents, which usually results in recurrent angina or even MI [73,74]. The introduction of new-generation drug-eluting stents (DESs) has dramatically attenuated this problem with locally released immunomodulatory and/or anti-proliferative agents, but considering the large population treated with DESs, the rate of ISR is still non-ignorable [75–78]. Currently, the optimal treatment for ISR has not reached a consensus. A variety of approaches such as balloon angioplasty, cutting or scoring balloon, DESs, and bypass grafting surgery are utilized in clinics, but they all demand extra invasive operations [79]. Under conditions of restenosis, the activated endothelium shows an up-expression of adhesion markers, like P-selectin, E-selectin, and vascular cell adhesion molecule [6], resulting in the targeting and further adhering of circulating platelets. PITD can mimic this reaction by attaching man-made ligands or cloaking with platelet membrane, and then release antiproliferative drugs in appropriate amounts at the site of restenosis.

1.3.1. Platelet mimics

Under restenotic conditions, targeting endothelium with nanoparticles to deliver the drug attracts the main attention. Lin et al. [80] imitated platelet binding ability towards activated endothelium by conjugating nanoparticles with GPIba, known for its platelet adhesion under high shear stress conditions, the predominant and special hemodynamic of lumen stenosis [81]. Then for practical use, nanoparticles made by degradable material PLGA carry dexamethasone, a widely used immune suppressant to reduce the intimal hyperplasia [82]. When reaching restenotic sites, these platelet-mimicking nanoparticles can adhere to both P-selectin which is highly expressed on damaged endothelial cells [83], and vWF deposited on subendothelial matrix [84]. Compared with their naked counterpart, these GPIba-conjugated nanoparticles exhibit a higher targeted and controlled drug delivery ability to the restenotic site, and further in vivo verification is needed before the actual clinical application.

1.3.2. Platelet membrane cloaking

Traditional anti-restenosis agents inhibit ISR at the cost of undifferentiated delayed arterial endothelialization, activating local immune reaction, and pro-thrombogenic environments, leading to suppression of neointimal hyperplasia and re-endothelialization [85,86]. A recently developed PITD for anti-stenosis treatment focuses on the site-targeting ability of platelet membranes to deliver novel anti-restenosis agents. Based on nanoclusters (loaded with a cell-permeable small molecule JQ1, a novel anti-restenosis inhibitor with unique endothelial protecting function [87]), which are coated with platelet membranes, Wang et al. [88] create an endothelium-protective anti-restenotic system by combining small molecule JQ1 and PITD. These nanoclusters are intravenously injected in the rat models of restenosis with the traditional anti-restenosis agent rapamycin as control. The results show that both JQ1 and rapamycin-loaded nanoclusters obviously suppress neointimal hyperplasia, but JQ1-loaded nanoclusters concurrently preserve the recovering ability of the endothelium, while the re-endothelialization of the rapamycin-loaded group is significantly inhibited. Because vascular restenosis is closely related to the inflammatory reactions in the injured area, Li et al. [89] prepare the platelet membrane-coated nanoparticle loaded with an anti-inflammatory cytokine IL-10. The ability to target vascular restenosis and regulate macrophage polarization has been demonstrated, eventually exerting the anti-restenosis effect in a rat model of angioplasty-induced vascular injury. Overall, these novel designs provide an endothelium-protective and inflammation-reduced anti-restenosis therapy via innovations in both drug and delivery methods, which are promising to be available for anti-restenosis therapy in clinics.

1.4. PITD for imaging of atherosclerosis

Atherosclerotic plaque is the most common culprit of CHD [90]. As to the assessment of plaque progression, noninvasive imaging means are of great importance. However, the existing technologies and tools like coronary computed tomography angiography provide just physical detections of coronary lesions, rather than biological development of the plaques. In order to provide a better imaging method for the diagnosis and assessment of atherosclerotic lesions, biomimetic nanoparticles are prepared by coating platelet membranes around a synthetic nanoparticulate core containing magnetic resonance imaging (MRI) contrast agents inside. The platelet membrane-coated nanoparticles (PNPs) can be used to distinguish the presence of plaques from surrounding zones with MRI scanning. Except for regions with clear plaque formation, subclinical areas of arteries susceptible to plaque formation can also be distinguished [91]. In order to early detect atherosclerosis, A platelet membrane with foam cell targeting is wrapped around the naphthalimide-based fluorescent probe for recognition of cellular reactive oxygen species (ROS). Under the recognition of intracellular ROS, fluorescence signals can be observed in the thoracic aorta of early atherosclerotic rats. Compared with other diagnostic methods, this strategy can be used to offer physicians additional information about the asymptomatic stage (the stage of foam cell formation without the plaques taking shape) and facilitate optimal decision-making in clinical practice.

1.5. Limitation and perspective

Despite significant progress in PITD-related research, to translate PITD into practical application, there are still existing issues including safety, efficiency, and production need to be addressed. Firstly, the risk of thrombosis must be thoroughly evaluated because of platelet thrombogenic function. Secondly, the possibility of immunological attack introduced by synthetic components still exists for platelet mimics, which also needs to be prudently considered. Thirdly, practical issues like production, storage, and transportation need proper settlements. For the future direction of PITD, the most important issue is that a more intelligent PITD will be developed to achieve personalized treatment by taking into account individual differences among patients. In addition, gene editing technology will be used to modify molecules on the surface of platelet membranes to enhance their targeting and delivery capabilities. Moreover, the development of platelet-mimicking particles can reach commercial production more easily because of their pure human-made materials.

2. Conclusion

The present review demonstrates the strategy of utilizing the targeting and adhesion ability of platelets to facilitate drug delivery for the treatment of CHD. Agents or therapeutic cells can be protected from blood dispersion and directed to aimed sites by hitchhiking live platelets, leveraging platelet membranes, and mimicking platelet function. These PITD designs benefit from an enhanced understanding of the biological properties of platelets and the rapid development of formation engineering and chemical conjugating technologies. Given the serious burden of CHD worldwide, further investigations of PITD strategy are required before accelerating into clinical translation.

Ethics requirement

Not applicable.

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Data availability statement

No data was used for the research described in the article.

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Yu Jiang: Writing – original draft. **Zhi-Yao Wei:** Writing – review & editing. **Zhi-Feng Song:** Writing – review & editing. **Hai-Yan Qian:** Writing – review & editing.

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.

References

[1] P. J, D. L, M. M, S.S. A, J.D. S, K. T, et al., Reducing the global burden of cardiovascular disease, Part 1: the epidemiology and risk factors 121 (6) (2017) 677–694.
[2] K.M. Broughton, B.J. Wang, F. Firouzi, F. Khalafalla, S. Dimmeler, F. Fernandez-Aviles, et al., Mechanisms of cardiac repair and regeneration, Circ. Res. 122 (8) (2018) 1151–1163.
[3] T. D, A. H, P. S, B. Ro, P. K, V. F, et al., PCI and CABG for treating stable coronary artery disease: JACC review, Topic of the Week 73 (8) (2019) 964–976.
[4] P. X, S. F, P. Nhj, W.F. F, E. B, T. Pal, et al., Five-year outcomes with PCI guided by fractional flow reserve 379 (3) (2018) 250–259.
[5] P. M, E. O, S.M.J.B. science, Overview of the Latest Developments in the Field of Drug-Eluting Stent Technology, 2019 undefined(undefined):undefined.
[6] D. Gd, B.E. C, A. C, S. Ea, G.S. M, Cardiology MRJJotACo. In-stent restenosis in the drug-eluting stent era 56 (23) (2010) 1897–1907.
[7] T.F. L, J. S, E. Fr, M. J, G. N, T. Fc, et al., Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications 115 (8) (2007) 1051–1058.
[8] K. Kc, U. Gj, S. W, T. Gj, journal Rljeh, Intracoronary imaging of coronary atherosclerosis: validation for diagnosis, prognosis and treatment, 35a-c 37 (6) (2016) 524.
[9] Q.H. Z C, research Gzjaoc, Leveraging Engineering of Cells for Drug Delivery 51 (3) (2018) 668–677.
[10] S.M. K, P.H. F, Society SJJJocrojotCR. Overcoming key biological barriers to cancer drug delivery and efficacy 267 (undefined) (2017) 15–30.
[11] L.R.J. Nature, Drug delivery and targeting 392 (null) (1998) 5–10.
[12] R.C. Becker, T. Sexton, S.S. Smyth, Translational implications of platelets as vascular first responders, Circ. Res. 122 (3) (2018) 506–522.
[13] S. Ek, H. P, J.Y. N, L. Km, Biomolecules CJJ, therapeutics, Platelet Shape Changes and Cytoskeleton Dynamics as Novel Therapeutic Targets for Anti-Thrombotic Drugs 25 (3) (2017) 223–230.
[14] M.R. Dp, L. S, A. C, reviews Ncjtm, Platelet derivatives in regenerative medicine: an update 29 (1) (2015) 52–61.
[15] Y. Lu, Q. Hu, C. Jiang, Z. Gu, Platelet for drug delivery, Curr. Opin. Biotechnol. 58 (2019) 81–91.
[16] M. Shafiq, Y. Jung, S.H. Kim, Insight on stem cell preconditioning and instructive biomaterials to enhance cell adhesion, retention, and engraftment for tissue repair, Biomaterials 90 (2016) 85–115.
[17] V. Sp, delivery Vbjeood, Targeted delivery of thrombolytic agents: role of integrin receptors 6 (5) (2009) 499–508.
[18] S.M. P, R. J-E, M. G, P. Mr, F. Ga, A. A, et al., Stem cell therapy: a novel approach for myocardial infarction 234 (10) (2019) 16904–16912.
[19] S.B. O, S. H-R, C.-A. Ge, M. Rt, K. Xy, C.-F. Ha, et al., Inflammation following acute myocardial infarction: multiple players, dynamic roles, and novel therapeutic opportunities 186 (undefined) (2018) 73–87.
[20] C.P. Hodgkinson, A. Bareja, J.A. Gomez, V.J. Dzau, Emerging concepts in paracrine mechanisms in regenerative cardiovascular medicine and biology, Circ. Res. 118 (1) (2016) 95–107.
[21] T. T, J. B, P.A. P-W, V. Hd, Cardiology AsjjotACo, The dying stem cell hypothesis: immune modulation as a novel mechanism for progenitor cell therapy in cardiac muscle 46 (10) (2005) 1799–1802.
[22] M. Gyongyosi, W. Wojakowski, E.P. Navarese, L.A. Moye, A. Investigators, Meta-analyses of human cell-based cardiac regeneration therapies: controversies in meta-analyses results on cardiac cell-based regenerative studies, Circ. Res. 118 (8) (2016) 1254–1263.
[23] D. H, Y. Ea, T.J. B, P. Z, P. R, Et P, et al., Radiolabeled cell distribution after intramyocardial, intracoronary, and interstitial retrograde coronary venous delivery: implications for current clinical trials 112 (null) (2005) I150–I156.
[24] A.A. W B, M. Z, C. B, S. M, B. A, et al., Assessment of the tissue distribution of transplanted human endothelial progenitor cells by radioactive labeling 107 (16) (2003) 2134–2139.
[25] J.N. T, J. C, K. H, C. Xl, L. L, Z. Jy, et al., Concise review: is cardiac cell therapy dead? Embarrassing Trial Outcomes and New Directions for the Future 7 (4) (2018) 354–359.
[26] B. V, B.E. C, S.V. A, D. C, D.J. C, E. G, et al., ST-segment elevation myocardial infarction 5 (1) (2019) 39.
[27] D. A, reviews Rmjhf, Nitric oxide, platelet function, myocardial infarction and reperfusion therapies 8 (1) (2003) 47–54.
[28] I. P, A.M. L, D.M. Gl, C. Hc, A. T, C. C, et al., Are endothelial progenitor cells mobilized by myocardial ischemia or myocardial necrosis? A cardiac magnetic resonance study 216 (2) (2011) 355–358.

[29] K. S, B. B, O. B, F. P, A. E, S. S, et al., Circulating platelet-progenitor cell coaggregate formation is increased in patients with acute coronary syndromes and augments recruitment of CD34+ cells in the ischaemic microcirculation 34 (32) (2013) 2548–2556.
[30] B. U, K.R.J. mAbs, The making of bispecific antibodies 9 (2) (2017) 182–212.
[31] M. Ziegler, X. Wang, B. Lim, E. Leitner, F. Klingberg, V. Ching, et al., Platelet-targeted delivery of peripheral blood mononuclear cells to the ischemic heart restores cardiac function after ischemia-reperfusion injury, Theranostics 7 (13) (2017) 3192–3206.
[32] M. Ziegler, K. Haigh, T. Nguyen, X. Wang, B. Lim, M.L. Yap, et al., The pulmonary microvasculature entraps induced vascular progenitor cells (iVPCs) systemically delivered after cardiac ischemia-reperfusion injury: indication for preservation of heart function via paracrine effects beyond engraftment, Microcirculation 26 (2) (2019) e12493.
[33] L. Y, V. O, P. Yf, A. D, E. B, M. E, et al., Induction of vascular progenitor cells from endothelial cells stimulates coronary collateral growth 110 (2) (2012) 241–252.
[34] P. Mungchan, K. Glab-Ampai, N. Chruewkamlow, K. Trakarnsanga, C. Srisawat, K.T. Nguyen, et al., Targeted nanoparticles for the binding of injured vascular endothelium after percutaneous coronary intervention, Molecules 27 (23) (2022).
[35] Z. L, Z. L, Z. C, E. J, W. L, J. R, et al., Bioorthogonal chemistry for selective recognition, separation and killing bacteria over mammalian cells 52 (17) (2016) 3482–3485.
[36] Z. Li, D. Shen, S. Hu, T. Su, K. Huang, F. Liu, et al., Pretargeting and bioorthogonal click chemistry-mediated endogenous stem cell homing for heart repair, ACS Nano 12 (12) (2018) 12193–12200.
[37] D. Shen, Z. Li, S. Hu, K. Huang, T. Su, H. Liang, et al., Antibody-armed platelets for the regenerative targeting of endogenous stem cells, Nano Lett. 19 (3) (2019) 1883–1891.
[38] J. Tang, T. Su, K. Huang, P.U. Dinh, Z. Wang, A. Vandergriff, et al., Targeted repair of heart injury by stem cells fused with platelet nanovesicles, Nat. Biomed. Eng. 2 (2018) 17–26.
[39] J. Lader, M. Stachel, L. Bu, Cardiac stem cells for myocardial regeneration: promising but not ready for prime time, Curr. Opin. Biotechnol. 47 (2017) 30–35.
[40] R.T. Lee, Adult cardiac stem cell concept and the process of science, Circulation 138 (25) (2018) 2940–2942.
[41] K. Kretzschmar, Y. Post, M. Bannier-Helaouet, A. Mattiotti, J. Drost, O. Basak, et al., Profiling proliferative cells and their progeny in damaged murine hearts, Proc Natl Acad Sci U S A 115 (52) (2018) E12245–E12254.
[42] R.J. Vagnozzi, M. Maillet, M.A. Sargent, H. Khalil, A.K. Johansen, J.A. Schwanekamp, et al., An acute immune response underlies the benefit of cardiac stem-cell therapy, Nature (2019).
[43] R. K, K.M.J.C. research, More than tiny sacks: stem cell exosomes as cell-free modality for cardiac repair 118 (2) (2016) 330–343.
[44] R. K, A.A. R, D. Gj, L.S.J.B. pharmacology, Harnessing the secretome of cardiac stem cells as therapy for ischemic heart disease 113 (undefined) (2016) 1–11.
[45] T. Su, K. Huang, H. Ma, H. Liang, P.U. Dinh, J. Chen, et al., Platelet-inspired nanocells for targeted heart repair after ischemia/reperfusion injury, Adv. Funct. Mater. (2018).
[46] T. Zhou, X. Yang, T. Wang, M. Xu, Z. Huang, R. Yu, et al., Platelet-membrane-encapsulated carvedilol with improved targeting ability for relieving myocardial ischemia-reperfusion injury, Membranes 12 (6) (2022).
[47] J.R. Chevillet, Q. Kang, I.K. Ruf, H.A. Briggs, L.N. Vojtech, S.M. Hughes, et al., Quantitative and stoichiometric analysis of the microRNA content of exosomes, Proc Natl Acad Sci U S A 111 (41) (2014) 14888–14893.
[48] I. Sukma Dewi, S. Celik, A. Karlsson, Z. Hollander, K. Lam, J.W. McManus, et al., Exosomal miR-142-3p is increased during cardiac allograft rejection and augments vascular permeability through down-regulation of endothelial RAB11FIP2 expression, Cardiovasc. Res. 113 (5) (2017) 440–452.
[49] Q. Li, Z. Huang, Q. Wang, J. Gao, J. Chen, H. Tan, et al., Targeted immunomodulation therapy for cardiac repair by platelet membrane engineering extracellular vesicles via hitching peripheral monocytes, Biomaterials 284 (2022) 121529.
[50] X. Weng, H. Tan, Z. Huang, J. Chen, N. Zhang, Q. Wang, et al., Targeted delivery and ROS-responsive release of Resolvin D1 by platelet chimeric liposome ameliorates myocardial ischemia-reperfusion injury, J. Nanobiotechnol. 20 (1) (2022) 454.
[51] Q. Li, Y. Song, Q. Wang, J. Chen, J. Gao, H. Tan, et al., Engineering extracellular vesicles with platelet membranes fusion enhanced targeted therapeutic angiogenesis in a mouse model of myocardial ischemia reperfusion, Theranostics 11 (8) (2021) 3916–3931.
[52] J. Jiang, L. Ni, X. Zhang, H. Wang, L. Liu, M. Wei, et al., Platelet membrane-fused circulating extracellular vesicles protect the heart from ischemia/reperfusion injury, Adv. Healthcare Mater. (2023) e2300052.
[53] J. S, L. Ca, S. A, A. J, F. Ka, D.I.J. Circulation, Increased platelet binding to circulating monocytes in acute coronary syndromes 105 (18) (2002) 2166–2171.
[54] B. Cheng, E.K. Toh, K.H. Chen, Y.C. Chang, C.J. Hu, H.C. Wu, et al., Biomimicking platelet-monocyte interactions as a novel targeting strategy for heart healing, Adv. Healthcare Mater. 5 (20) (2016) 2686–2697.
[55] H. Tan, Y. Song, J. Chen, N. Zhang, Q. Wang, Q. Li, et al., Platelet-like fusogenic liposome-mediated targeting delivery of miR-21 improves myocardial remodeling by reprogramming macrophages post myocardial ischemia-reperfusion injury, Adv. Sci. (2021) e2100787.
[56] D.B. B, D. Rn, M.R. C, K.S.J.V. pharmacology, Plasminogen activators: a comparison 44 (1) (2006) 1–9.
[57] I. G, targets Tsjeoot, Tissue-type plasminogen activator as a therapeutic target in stroke 12 (2) (2008) 159–170.
[58] S. L, X. F, R. J, delivery Lgjeood, Tissue plasminogen activator-based nanothrombolysis for ischemic stroke 15 (2) (2018) 173–184.
[59] Y.H. Ma, C.H. Liu, Y. Liang, J.P. Chen, T. Wu, Targeted delivery of plasminogen activators for thrombolytic therapy: an integrative evaluation, Molecules 24 (18) (2019).
[60] H.K. Y U, J. J, Y. S, Society TYJJocrojotCR. An ultrasound-responsive nano delivery system of tissue-type plasminogen activator for thrombolytic therapy 147 (2) (2010) 269–277.
[61] C.L. Pawlowski, W. Li, M. Sun, K. Ravichandran, D. Hickman, C. Kos, et al., Platelet microparticle-inspired clot-responsive nanomedicine for targeted fibrinolysis, Biomaterials 128 (2017) 94–108.
[62] K.K. St G, T. B, J. C, K. A, L. Ls, et al., Multifunctional thrombin-activatable polymer capsules for specific targeting to activated platelets 27 (35) (2015) 5153–5157.
[63] B. Dl, biomechanics Kdjjo, Wall shear over high degree stenoses pertinent to atherothrombosis 43 (15) (2010) 2970–2977.
[64] M.H. K, therapy Fsjeroc, Targeting shear stress-induced platelet activation: is lesion-specific antiplatelet therapy a realistic clinical goal? 3 (5) (2005) 941–951.
[65] N. K, M. K, M. Bd, M. C, A. B, T. M, et al., Shear-activated nanotherapeutics for drug targeting to obstructed blood vessels 337 (6095) (2012) 738–742.
[66] M.G. M, N. K, G. Mj, O. U, S. V, L. Et, et al., Shear-activated nanoparticle aggregates combined with temporary endovascular bypass to treat large vessel occlusion 46 (12) (2015) 3507–3513.
[67] Q. Hu, C. Qian, W. Sun, J. Wang, Z. Chen, H.N. Bomba, et al., Engineered nanoplatelets for enhanced treatment of multiple myeloma and thrombus, Adv Mater 28 (43) (2016) 9573–9580.
[68] M. Z, E. A, B. B, A.B. R D, A.V. G, et al., Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy 98 (5) (2001) 1614–1615.
[69] Y. Zhao, R. Xie, N. Yodsanit, M. Ye, Y. Wang, B. Wang, et al., Hydrogen peroxide-responsive platelet membrane-coated nanoparticles for thrombus therapy, Biomater. Sci. 9 (7) (2021) 2696–2708.
[70] X. Guo, T. Hong, J. Zang, R. Shao, X. Hou, K. Wang, et al., Thrombus-specific/responsive biomimetic nanomedicine for spatiotemporal thrombolysis and alleviation of myocardial ischemia/reperfusion injury, J. Nanobiotechnol. 20 (1) (2022) 531.
[71] B. Liu, F. Victorelli, Y. Yuan, Y. Shen, H. Hong, G. Hou, et al., Platelet membrane cloaked nanotubes to accelerate thrombolysis by thrombus clot-targeting and penetration, Small 19 (4) (2023) e2205260.
[72] R. V, lipidology Fajcoi, Pathology of in-stent restenosis 10 (6) (1999) 499–506.
[73] J.W. J, T.A. A, J.J. V, Cardiology QPJNr. Restenosis after PCI. Part 2: prevention and therapy 9 (2) (2011) 79–90.
[74] J.W. J, J.J. V, T.A. A, Cardiology QPJNr. Restenosis after PCI. Part 1: pathophysiology and risk factors 9 (1) (2011) 53–62.

[75] L. L, B. L, J. R, G. H, C. Q, disorders Wjjbc, Comparison of drug-eluting balloon versus drug-eluting stent for treatment of coronary artery disease: a meta-analysis of randomized controlled trials 18 (1) (2018) 46.
[76] H. K, K. O, T. K, P.G. Y, A.J. L, J.J. P, et al., Impact of stent size selection on acute and long-term outcomes after drug-eluting stent implantation in de Novo coronary lesions, undefined 10 (10) (2017).
[77] D.M. C, V. Mr, S. Ts, L. Af, N. Sl, Foundation MljajokdtojotNK, Long-term clinical outcomes following drug-eluting or bare-metal stent placement in patients with severely reduced GFR: results of the Massachusetts Data Analysis Center (Mass-DAC) State Registry 57 (2) (2011) 202–211.
[78] C. R, P. S, A. B, P. L, M.G.J. Heart, Drug eluting stents: an updated meta-analysis of randomised controlled trials 92 (5) (2006) 641–649.
[79] D. G, G. G, P. A, P. C, C. T, C.D.J. Bmj, Treatment strategies for coronary in-stent restenosis: systematic review and hierarchical Bayesian network meta-analysis of 24 randomised trials and 4880 patients 351 (undefined) (2015) h5392.
[80] A. Lin, A. Sabnis, S. Kona, S. Nattama, H. Patel, J.F. Dong, et al., Shear-regulated uptake of nanoparticles by endothelial cells and development of endothelial-targeting nanoparticles, J. Biomed. Mater. Res. 93 (3) (2010) 833–842.
[81] J.M. Cosemans, A. Angelillo-Scherrer, N.J. Mattheij, J.W. Heemskerk, The effects of arterial flow on platelet activation, thrombus growth, and stabilization, Cardiovasc. Res. 99 (2) (2013) 342–352.
[82] S. Kona, J.F. Dong, Y. Liu, J. Tan, K.T. Nguyen, Biodegradable nanoparticles mimicking platelet binding as a targeted and controlled drug delivery system, Int. J. Pharm. 423 (2) (2012) 516–524.
[83] Z. L, M.K. D, O.B. Ka, Du X %J Arteriosclerosis t, biology v. Signaling during platelet adhesion and activation 30 (12) (2010) 2341–2349.
[84] medicine Rzjao, Role of von Willebrand factor in platelet thrombus formation, 2000, pp. 2–9, null(undefined).
[85] F. P, S. A, M.C. B, M. B, S.S. G, T. Em, et al., Stent thrombosis with second-generation drug-eluting stents compared with bare-metal stents: network meta-analysis of primary percutaneous coronary intervention trials in ST-segment–elevation myocardial infarction [corrected] 7 (1) (2014) 49–61.
[86] M. J, A.V. F, A. F, M. Ek, F.D. K, E. L, et al., Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk 48 (1) (2006) 193–202.
[87] P. F, J. Q, S. P, Y. S, S. Wb, O. F, et al., Selective inhibition of BET bromodomains 468 (7327) (2010) 1067–1073.
[88] B. Wang, G. Chen, G. Urabe, R. Xie, Y. Wang, X. Shi, et al., A paradigm of endothelium-protective and stent-free anti-restenotic therapy using biomimetic nanoclusters, Biomaterials 178 (2018) 293–301.
[89] F. Li, Z. Rong, R. Zhang, S. Niu, X. Di, L. Ni, et al., Vascular restenosis reduction with platelet membrane coated nanoparticle directed M2 macrophage polarization, iScience 25 (10) (2022) 105147.
[90] C. W, N.H.J.N. medicine, Atherosclerosis: current pathogenesis and therapeutic options 17 (11) (2011) 1410–1422.
[91] X. Wei, M. Ying, D. Dehaini, Y. Su, A.V. Kroll, J. Zhou, et al., Nanoparticle functionalization with platelet membrane enables multifactored biological targeting and detection of atherosclerosis, ACS Nano 12 (1) (2018) 109–116.