Expert Opinion

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Targeted delivery of thrombolytic agents: role of integrin receptors

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Blood clotting (formation of thrombus) plays a critical role in the evolution of a number of cardiovascular diseases. Targeted delivery of thrombolytic agents reduces the risks of hemorrhage and toxicity associated with systemic drug administration, thus offering a promising, minimally invasive approach to controlling and treating thrombosis. Platelets play a major role in the progression of thrombosis on vascular injury. Platelet integrin αIIbβ3 (GP IIb/IIIa) serves as a receptor for various proteins such as fibrinogen, vWF, fibronectin and vitronectin, as well as contributing to the adhesion and aggregation of platelets in a variety of conditions. These receptor-based targeted therapies are currently under clinical studies. Integrins and RGD-based ligands for integrins are currently being investigated in imaging and drug delivery related areas of research. RGD-targeted drugs and imaging agents have been developed either by direct conjugation of the homing peptide to the drug or by conjugation of the RGD-peptide to a carrier device containing drug molecules. This review describes the role of integrin receptors in the pathophysiology of thrombosis and its use in the targeted delivery of thrombolytic agents.

Keywords: integrin receptors, platelet, targeting, thrombolytic agents

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1. Introduction

Cardiovascular diseases are typically localized to discrete vascular regions, affording great opportunity for targeted pharmacological treatment. Vascular thrombosis is a major clinical problem, particularly in developed Western countries. Indeed, vascular thrombosis accounts for about half of all deaths in these countries as a result of myocardial infarction, stroke, pulmonary emboli and the like. The best way to improve patient survival and decrease morbidity is prompt detection and treatment of thrombosis with thrombolytic therapy. Therefore, a variety of thrombolytic agents such as streptokinase, urokinase and tissue plasminogen activator (t-PA) have been developed. These thrombolytic agents work by activating the protein plasminogen into plasmin. When this occurs, activated plasmin circulates throughout the vascular system, triggering the fibrinolytic cascade that dissolves the thrombi [1].

However, the use of the above-described thrombolytic agents in humans also leads to many side effects. Therefore, more research is required to address the many problems involving their effectiveness and potentially harmful side effects [2].

Targeted drug delivery holds a promising outlook for the treatment of vascular injury-associated thrombotic and occlusive events caused by cardiovascular diseases or interventional procedure. Current strategies for targeted delivery, that is *trans*-catheter or drug eluting stent techniques, are expensive and suffer from the limitations of early drug washout, reduced control on drug concentration and late-stage thrombosis [3]. For optimal drug delivery, delivery systems should be localized to the site of thrombus and should maintain a reservoir which avoids

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uptake into unwanted tissue. Therefore, novel drug delivery systems, surface modified with targeting moiety for targeted delivery of thrombolytic agents to and localizing at the particular site of thrombus, may provide an effective alternative.

Platelets, much more than a passive, circulating, anuclear cellular element, play a vital role in various thromboembolic diseases [4]. Under normal conditions, platelets circulate freely in blood vessels without interacting with other platelets or the vascular endothelium. However, at the site of endothelial damage, whether from vascular injury or rupture of an atherosclerotic plaque, blood platelets come into contact with the subendothelial extracellular matrix, which leads to a chain of reactions and the formation of a platelet-rich hemostatic plug. There are various surface receptors on the platelets (**Table 1**) which play an important role in the aggregation of platelets and thus have been used as a target site for the targeted therapy of thromboembolism [5].

Integrin receptors αIIbβ3 (also named as GP IIb/IIIa) have been used for targeted therapy of thrombosis by direct inhibition of these receptors. In the present review, the role of integrins in the formation of thrombus and their use in the targeted delivery of thrombolytic agents is discussed.

2. Targeted delivery of thrombolytic agents

2.1 Thrombosis: a major causative for cardiovascular diseases

When a blood vessel is injured, the body uses platelets and fibrin to form a blood clot, as the first step in repairing it to prevent loss of blood. Thrombosis is a process of blood clot formation which may obstruct the blood flow through the blood vessels in the circulatory system. The formation of thrombosis plays a critical role in the progression of a number of cardiovascular pathologies [6]. Three main categories of cardiovascular pathologies are: i) atherosclerotic heart disease (myocardial infarction); ii) cerebrovascular disease (stroke); and iii) venous thromboembolism (VTE) (deep vein thrombosis [DVT] and pulmonary embolism [PE]). Although the primary cause of myocardial or cerebral infarction is the atherosclerotic degeneration of the vessel wall. However, thrombotic occlusion of critically situated blood vessels is the key event that triggers the clinical syndrome. Venous thromboembolism, a silent yet potentially fatal disease, affects over 2 million Americans annually [7,8]. Various risk factors of VTE are:

- increasing age
- immobility (> 4 d), paralysis of legs
- previous VTE
- malignancy (pelvic, abdominal, metastatic)
- surgery
- trauma (pelvis, hip, legs)
- obesity
- varicose veins
- heart failure
- recent myocardial infarction
- inflammatory bowel disease
- nephritic syndrome
- pregnancy and postpartum
- high-dose estrogen therapy
- infection

2.2 Role of platelets integrin receptor αIIbβ3 on platelet aggregation and thrombus formation

Platelets play a key role in thrombosis and hemostasis, which can be either beneficial or deleterious depending on the circumstances [9]. The major physiological function of platelets is in hemostasis. However, in pathophysiologic conditions, platelet activation leads to a range of responses that play a critical role in arterial thrombosis.

Thrombosis is pathological excessive hemostasis, but its pathogenesis in the venous circulation differs from that in the arterial circulation. The venous circulation is primarily a low-shear system, and thrombi in venous thromboembolic disorders have an abundance of fibrin but a relative paucity of platelets. In contrast, arterial thrombi are platelet rich and result from endothelial injury in conditions of high shear.

Hemostatic platelets plug formation is the key event for the various thrombotic and ischemic diseases such as myocardial infarction, cerebral stroke and peripheral vascular diseases. This event results from a series of biochemical and cellular process that can be divided into four categories: adhesion, activation, secretion and aggregation (**Figure 1**). These processes have already been discussed in detail by various reviewers [10].

Membrane glycoprotein receptors are essential for platelet functions. These functions include platelet attachment to a diverse number of extracellular matrix proteins, including vWF, collagen, fibronectin and laminin [11]. Detailed descriptions of various integrin receptors have been made in earlier reviews [5]. Here a brief description of GP IIb/IIIa receptor is given. Platelet adhesion is a multi-step process in which attachment is followed by activation and spreading on the exposed surface [10]. The major receptor involved in the platelet adhesion is GP Ib, which is present in the platelet membrane in a tight complex with a low molecular weight component, GP IX. Activation of the GP IIb/IIIa receptor is the common pathway involved in platelet aggregation. GP IIb/IIIa is a heterodimeric platelet membrane receptor and the major integrin on the platelet surface. GP IIb consists of disulfide-linked heavy and light chains, whereas GP IIIa is a single-chain molecule. The two glycoproteins form a non-covalently linked, Ca^{2+}-dependent complex with 1:1 stoichiometry (**Figure 2**) [12,13]. The GP IIb/IIIa complex is normally present in an inactive state on resting platelets and serves as an adhesion receptor which has low affinity to surface-bound fibrinogen. However, these receptors result in a conformational change on platelet stimulation by physiologic ligands such as thrombin or collagen. This conformational change allows the platelet to bind to fibrinogen in plasma with high affinity. Fibrinogen binds two receptors simultaneously

Table 1. Surface membrane glycoprotein receptors involved in platelet adhesion and activation.

Receptors	Ligands	Functions
Leucin-rich protein		
GP Ib/IX	vWF, Thrombin	Adhesion
Integrins		
GP Ia/IIa ($\alpha 2\beta 1$)	Collagen	Adhesion
GP Ic/IIa ($\alpha 5\beta 1$)	Fibronectin	Adhesion
GP IIb/IIIa ($\alpha IIb\beta 3$)	Fibrinogen, vitronectin, fibronectin, vWF	Aggregation (secondary role in adhesion)
GP Ic/IIa ($\alpha 6\beta 1$)	Laminin	Adhesion
VnR ($\alpha v\beta 3$)	Vitronectin, fibrinogen	Adhesion

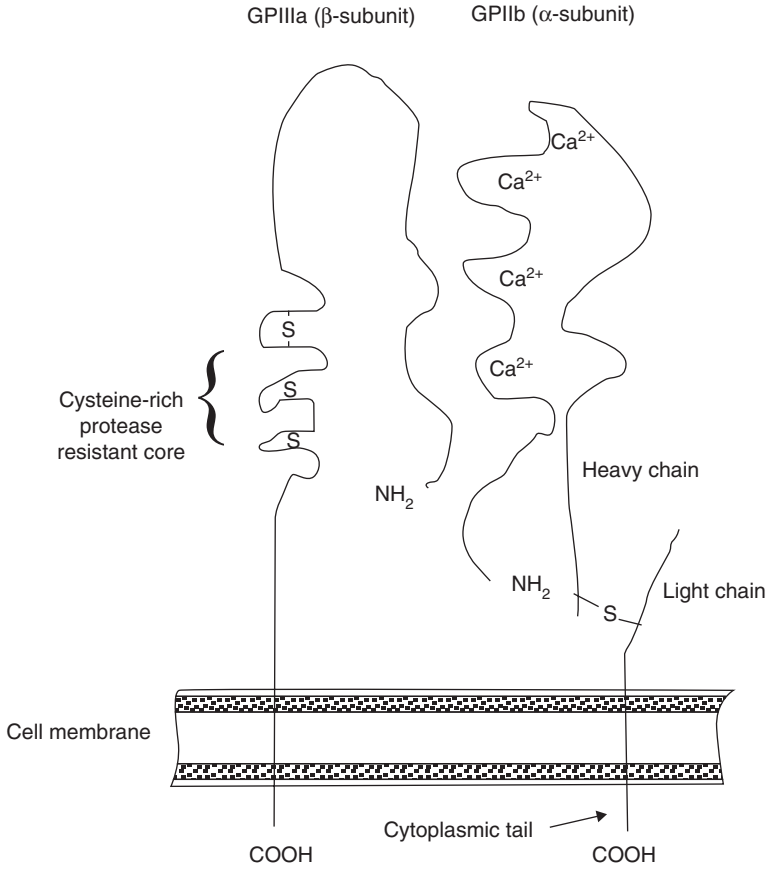

Figure 1. Structure of integrin (GPIIb/IIIa) receptor.

by binding to receptor patches on the surface of two different platelets, thus initiating platelet aggregation [12,14].

The bridging of adhered and activated platelets is mediated by the binding of fibrinogen through the RGD (Arg-Gly-Asp) motifs located at the two Aα chains and dodecapeptide sequences (HHLGGAKQAGDV) located within γ chains to the activated platelets via integrin $\alpha_{IIb}\beta_3$ (GPIIb/IIIa) [3,15]. Although fibrinogen can bind to GP IIb/IIIa by its RGD sequence, an amino acid sequence located at the carboxy-terminus of the gamma chain is primarily involved in its binding to GP IIb/IIIa. In addition, other RGD sequences are also present and mediate the interaction of several other ligands with GP IIb/IIIa [3]. Studies have revealed that mutation of the RGD sequence in vWF and vitronectin prevents their interaction with GP IIb/IIIa, confirming that RGD sequence is required for the interaction with platelets [16,17]. Thus, the RGD sequence could be an important tool for the manipulation of platelet binding and targeting.

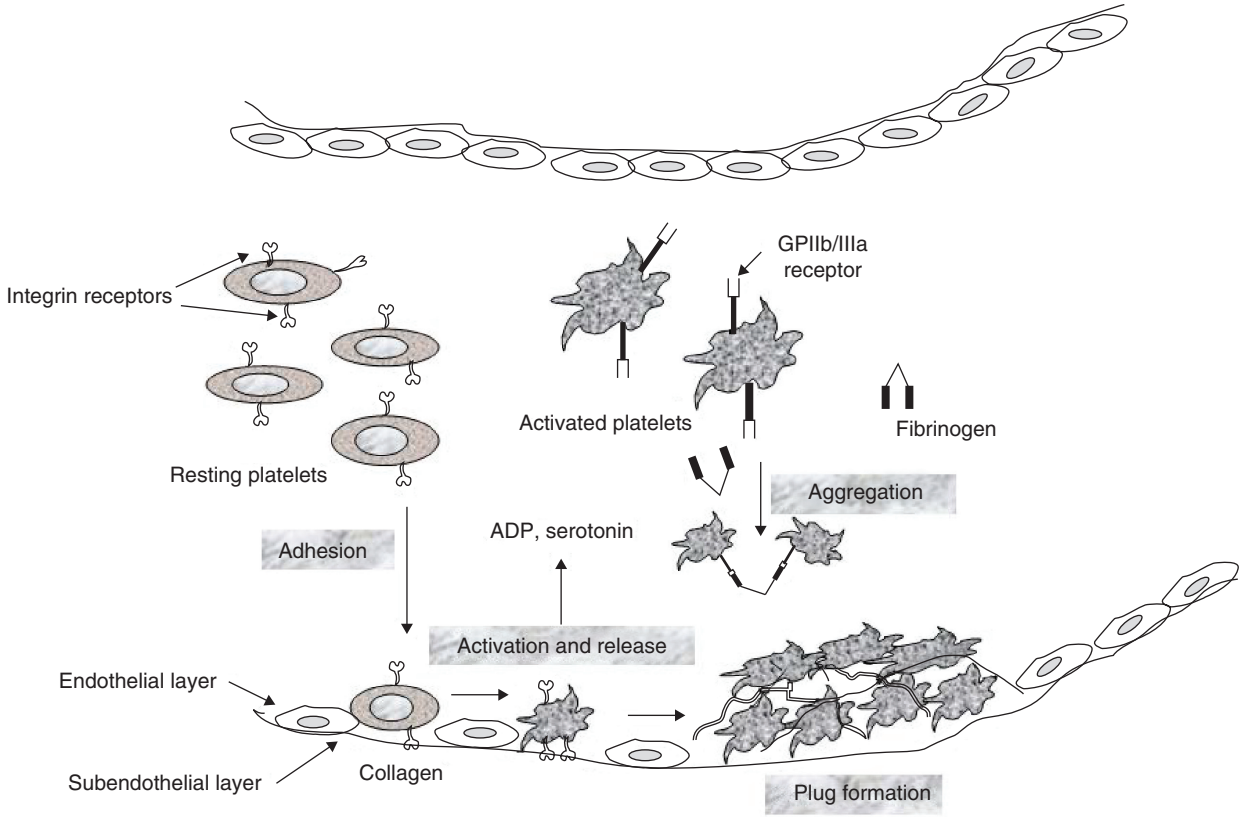

Figure 2. Mechanism for the formation of thrombus on the disruption of endothelial layer.

Activated platelets not only undergo aggregation, but also play an important role in the formation of fibrin through interaction with the extrinsic and intrinsic pathways of the coagulation cascade, which further contributes to stenosis and restenosis. During the conversion of prothrombin to thrombin, the prothrombin first attaches to prothrombin receptors on the platelets. This binding accelerates the formation of more thrombin from prothrombin through the release of cofactor (FV). Thrombin generated at the surface of activated platelets interacts with several secreted platelet proteins such as thrombospondin that modulate the coagulation response [18].

Platelet inhibition is a major strategy to prevent arterial thrombosis, but it is frequently associated with increased bleeding because of impaired primary hemostasis. Therefore, treatment of thrombotic disease requires optimal balance between prevention of new thrombotic events and management of bleeding complications [19].

The role of platelets in the formation of arterial thrombosis and the recognition of the GP IIb/IIIa receptor have directed considerable research effort toward the development of a novel class of thrombolytic agents based on GP IIb/IIIa receptor blockade, as well as targeted delivery of thrombolytic agents to the site of thrombus formation (**Figure 3**).

2.3 Antithrombotic agents based on GP IIb/IIIa receptor blockade

Regardless of the mechanism of activation, the final common pathway for platelet activation is the aggregation of platelets through fibrinogen bound to GP IIb/IIIa via the RGD sequence in the fibrinogen α-chain [20]. GP IIb/IIIa belongs to a superfamily of cell-surface receptors known as integrins that can recognize molecules carrying the RGD binding sequence in different conformations. Inhibition of platelet aggregation and avoidance of all the subsequent steps that lead to a thrombotic episode can be achieved by preventing the binding of fibrinogen to GP IIb/IIIa [21]. A number of potent GP IIb/IIIa antagonists have been developed for therapeutic use [22-24]. Since the fibrinogen-GP IIb/IIIa interaction is the final major step in platelet aggregation and GP IIb/IIIa is only expressed on platelets, it is clear that the development of GP IIb/IIIa antagonists is an attractive strategy for anti-platelet therapy with an expected strong and specific effect [5,25,26].

Abciximab is the chimeric Fab fragment of the murine antihuman GP IIb/IIIa MoAb developed by Coller [27]. It blocks ligand binding to GP IIb/IIIa through steric hindrance [28]. Abciximab is recommended as adjunct therapy in percutaneous coronary intervention (PCI), including balloon angioplasty, atherectomy and primary stent implantation [29]. Tirofiban

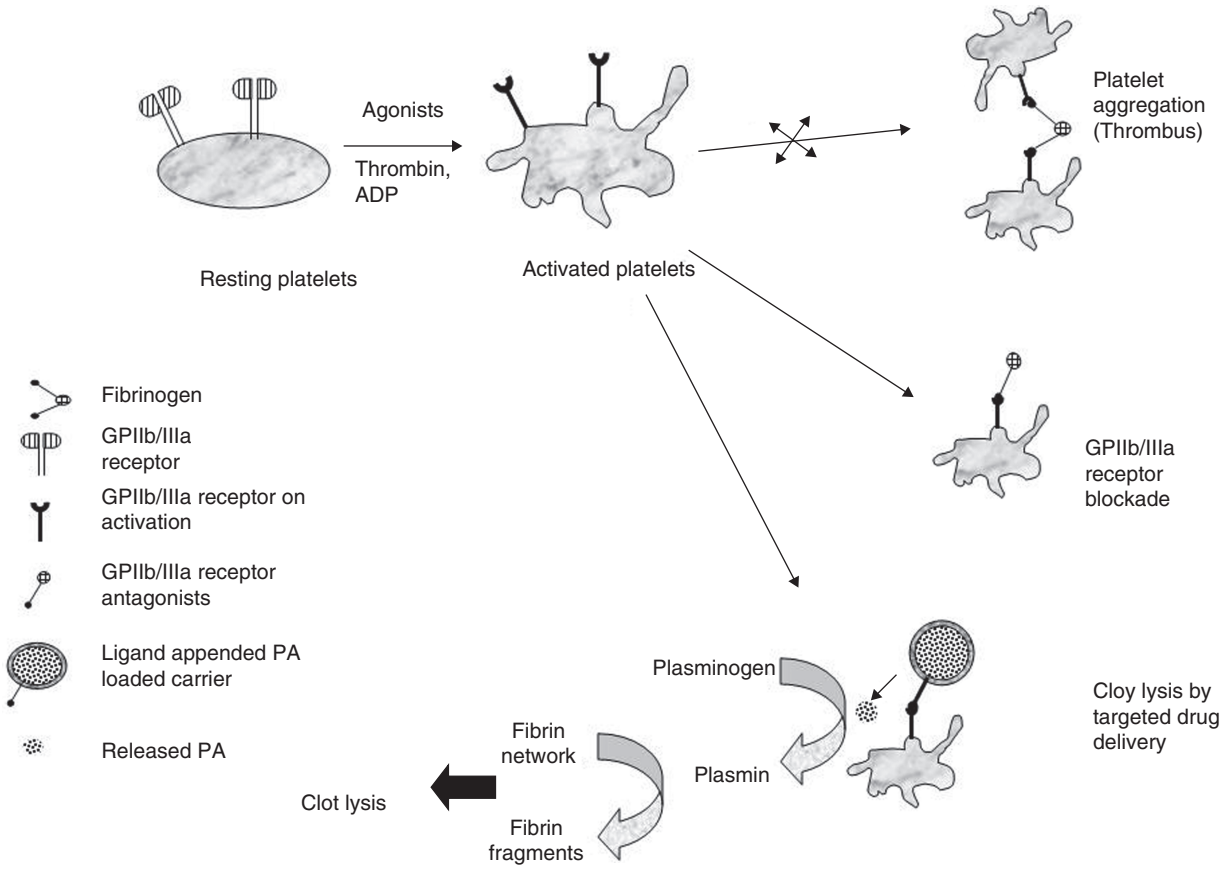

Figure 3. Schematic presentation showing the mechanism of action of different integrin targeted therapy.

is a specific non-peptide antagonist of GP IIb/IIIa that mimics the GP IIb/IIIa recognizing peptide RGD. It is effective in unstable angina and non-Q-wave myocardial infarction and protects patients undergoing coronary angioplasty for acute coronary syndromes. Eptifibatide is a cyclic hepta-peptide that mimics the KGD sequence of the snake venom barbourin. It effectively and safely reduces the acute adverse outcome of patients undergoing PCI and is also beneficial in unstable angina [5,30]. Because GP IIb/IIIa antagonists block platelet aggregation, they produce minor bleeding complications and thrombocytopenia [31,32].

2.4 GP IIb/IIIa receptor mediated targeted delivery of thrombolytic agents

The basic problems with conventional systemic drug administration are even biodistribution throughout the body and lack of specificity towards the target site. These problems necessitate large doses to achieve high local concentration. The high dose further increases the adverse side effects and non-specific toxicity. Drug targeting is the best approach to resolve these dose-related problems. Targeting may be either physical (pH and/or temperature dependent, magnetic targeting) or active (ligand–receptor interaction based targeting) [33,34]. The later approach provides the widest opportunities.

Based on these principles, various carrier systems have been constructed for the targeted delivery of therapeutic molecules to the various tissues and organs. The targeting moiety can be attached directly to an active moiety (therapeutic or diagnostic unit) or to the surface of soluble or insoluble carriers loaded with therapeutic molecules. Different reactive and biocompatible soluble polymers can be used as soluble carriers, whereas the family of insoluble carriers includes microparticles, nanoparticles, liposomes and micelles. Targeted delivery of imaging agent and thrombolytic agent are now among the most promising areas in both drug delivery and thrombolysis. The most promising construct to be used for targeting thrombi is a conjugate between diagnostic agents or thrombolytic agents and thrombus-specific targeting motifs. The above-described agents showed specificity towards the platelets integrin receptors (GP IIb/IIIa), and therefore it was speculated that these types of agents, that is anti-GP IIb/IIa antibody and/or RGD peptides, may also be used for targeted delivery

of thrombolytic agents to the site of platelet aggregation, that is thrombus [35].

The short half-life of thrombolytic drugs, usually between 3 and 20 min, necessitates the administration of high dosages of these agents in systemically active forms over an extended period of time, which, in turn, increases the risk of side effects such as uncontrolled hemorrhage. Other limitations of plasminogen activators include the rapid inactivation by components of the fibrinolytic system such as Plasminogen Activator Inhibitor-1 (PAI-1) and circulating antibodies.

Various techniques have been used to increase the half-life and to reduce the side effects of these agents. PEGylation [36] and novel carrier constructs such as liposomes [37-39] and polymeric particles [40-42] are most commonly used. Liposomal encapsulation of plasminogen activators might increase efficacy, improve selectivity, possibly reduce or eliminate antigenic complications, retard systemic deactivation of the agent and effectively lengthen the brief half-lifes of the agents [43]. Nguyen *et al.* [44] demonstrated *in vitro* the ability of liposomes to protect streptokinase in plasma without significant loss of protein activity. Liposome encapsulated streptokinase, urokinase and t-PA have all been studied for enhanced thrombolysis *in vivo* [45]. Plasminogen activators entrapped in liposomes have shown substantial reductions in the time required to obtain reperfusion and an increased digestion of thrombus as compared to freely infused plasminogen activators.

A second approach to prolong the biological half-life and improve the therapeutic potential of a thrombolytic agent is to prepare liposomes composed of distearolyphosphatidyl ethanolamine-N-poly (ethylene glycol) 2000 (DSPE-PEG_{2000}), that is stealth liposomes. Kim *et al.* [46] found that stealth liposomes increased the $T_{1/2}$ and AUC∞ of streptokinase up to 16.3 and 6.1-fold, respectively, and it was expected that longer thrombolytic activity might be achieved by long-circulating liposomes.

The successful design of novel thrombolytic agents depends on providing these agents with increased clot selectivity. It was demonstrated by Perkins *et al.* [47] that entrapment of tissue plasminogen activator into liposomes apparently provided the selective targeting needed to improve the efficacy of this fibrinolytic agent.

Further, Erdogan *et al.* [48] prepared three types of vesicular drug delivery systems, such as liposomes, niosomes and sphingosomes containing streptokinase, for achieving the slow release of entrapped proteins in the circulation to increase half-life, to mask immunogenic properties and to protect against loss of enzymatic activity. Biodistribution of these vesicular dispersions was monitored using radiolabelled streptokinase and compared with i.v. injected free streptokinase. The results demonstrated the highest label concentration of liposomes and sphingosomes in the spleen and kidneys. Detectable amounts of label were recovered from the thrombi in all three type of vesicles, with higher amounts at 4 hr than 1 hr. Uptake of Tc-99m-labelled streptokinase by the thrombus can be explained by the mechanism of thrombolysis produced by streptokinase. This mechanism involves a series of reactions where streptokinase adsorbs to and penetrates in and around the thrombus; it activates plasminogen located within the thrombus, and yields sufficient plasmin for fibrin dissolution and thrombolysis [49].

To further increase the targeting potential of thrombolytic agent to the specific site of thrombus, a specific ligand–receptor based approach has been used by various research groups [2,50,51]. Wang *et al.* [50] prepared thrombus-targeted RGD peptide conjugated urokinase liposomes and observed its thrombolytic efficacy on thrombus model rats. In this study the ligand H-Arg-Gly-Asp-Ser-OH (RGDS) conjugated DSPE-$PEG_{3,500}$-COOH was incorporated in liposomal lipid bilayers to produce thrombus-targeted long-circulatory liposomes. The thrombolytic activity was measured in terms of dry thrombi weights. It was observed that the targeted urokinase liposomes showed significantly improved thrombolytic efficacy as compared to conventional urokinase liposomes of the same dose ($P < 0.01$ in wet weights decrease and $P < 0.05$ in dry weights decrease respectively). A hypothetical mechanism for the improved thrombolytic activity of these types of carrier systems is depicted in **Figure 4**. It was demonstrated that urokinase was released selectively at the site of thrombus and acted by converting plasminogen to plasmin near the clot, thus reducing the bleeding complications.

For further increment in the affinity of RGD-conjugated liposomes to the activated platelets, conformationally constrained cyclic RGD peptides have been conjugated to the surface of liposomes [3], because it has been previously reported that cyclic RGD peptides showed higher specificity and affinity for GP IIb/IIIa receptor compared to linear RGD peptides [52].

Although liposomal encapsulation has proven to be an effective method for the delivery of thrombolytic drugs, a stability problem exists for such systems. Encapsulation of thrombolytic agents inside a protective polymeric carrier avoided drug deactivation during systemic circulation. In order to develop an encapsulated thrombolytic agent with an acceptable shelf life, Leach *et al.* [41] have entrapped a thrombolytic agent in both liposomes (LESK) and polymer microcapsules (MESK). Both formulations demonstrated reductions in reperfusion times, residual clot mass and improved return of flow compared to identical dosages of free streptokinase in a thrombosed rabbit carotid, with MESK resulting in comparable or even greater improvements. The mechanism for MESK has been explored by Leach *et al.* [40] using multiple microscopic techniques. MESK appears to resist adsorption to the leading edge of the thrombus, a common limitation for the permeation of free plasminogen activators. By avoiding adsorption and penetrating the thrombus, greater spatial distribution of the agent within the clot can be achieved.

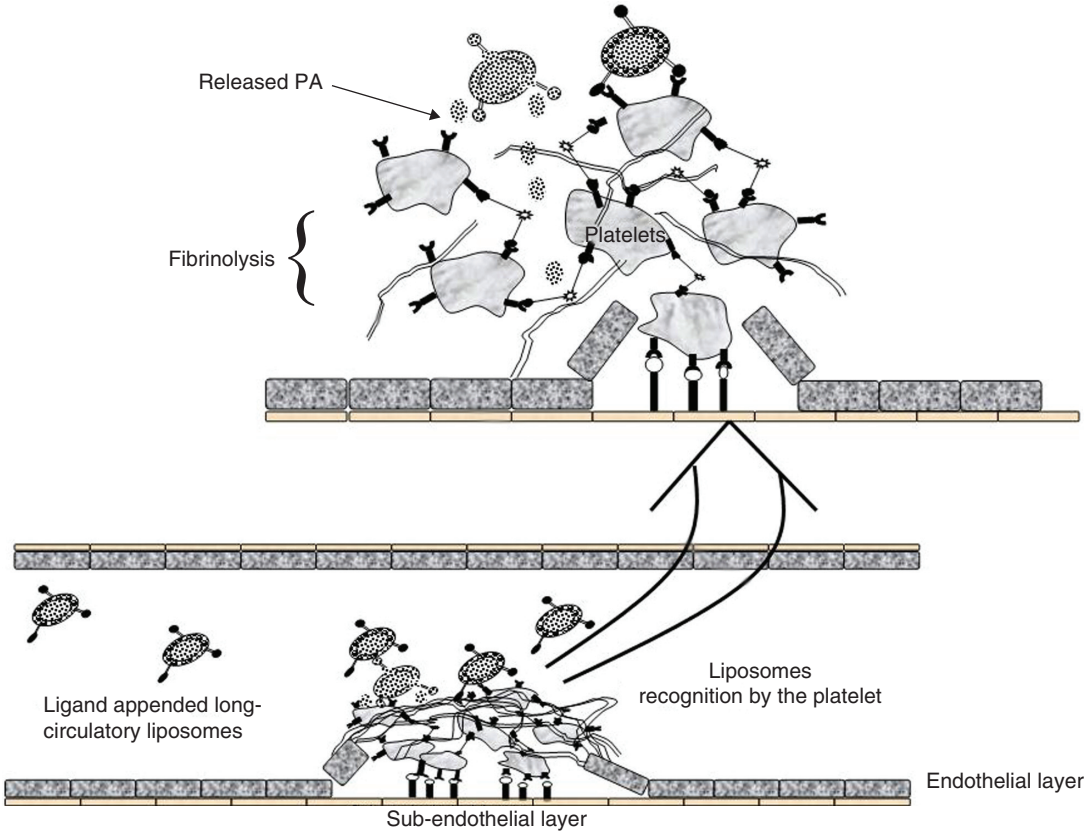

Figure 4. Hypotheticsl mechanism of clot lysis by ligand appended liposomes containing PA (ligand may be either antibody or RGD peptides).

The basic requirements for suitable polymeric thrombolytic carriers are: i) they should be small enough to circulate without the risk of vascular occlusion; ii) they should be tailored so that they accumulate at the site of thrombus either via physical targeting method (i.e., magnetite polymeric particle) or through ligand–receptor interactions; and iii) they must release thrombolytic agents in sufficient concentration to induce clot lysis.

Yumei *et al.* [53] exploited the use of microspheres composed of non-toxic poly(D,L-lactide-co-glycolide) (PLGA) and poly(D,L-lactide)-co-poly(ethylene glycol) (PLA-PEG) copolymers. The results demonstrated that microspheres could retain 5% tPA and released the drug at the site of thrombus at a concentration exceeding 4 mg/ml.

Recently, Kaminski *et al.* [54] prepared microspheres loaded with magnetite, which helps in the concentration of microspheres along with therapeutic moiety *in vivo* in the regions of thrombus formation using external permanent or superconducting magnets, thereby reducing the systemic dose and side effects.

The spheres were larger than is suitable for systemic delivery but they completely encapsulated the magnetic material and were able to release tPA to higher than theoretical thrombolysis concentrations. By modifying the synthesis parameters, the size of the particle might be reduced to the size of red blood cells for long systemic circulation.

The improved thrombolysis using liposomal or PEG microparticle-encapsulated plasminogen activator have been demonstrated by pressure-driven permeation to the clot interior [55]. However, in the absence of hydrodynamic pressure, the pores of fibrin clots are highly resistant to the permeation of carriers with a size of 1 μm or larger into the clot interior for clot lysis. Therefore there is a need to develop a system which permeates through the fibrin network into the interior of the clot for intra-clot lysis in the absence of pressure drop. Chung *et al.* [42] designed t-PA encapsulated nanoparticles (NPs) to enhance thrombolysis by applying electrostatic forces or ligand–receptor interactions between the NPs and blood clots. In this study t-PA-loaded PLGA NPs were prepared with chitosan (CS) and CS-GRGD coating and evaluated for thrombolysis capabilities in a blood clot-occluded tube model by determining clot lysis times and the masses of the digested clots. The PLGA/CS NPs showed the shortest clot lysis time and PLGA/CS-GRGD NPs showed the highest weight percentage of digested clots. The permeation results of the NPs in the blood clots demonstrated that PLGA/CS-GRGD NPs adhered more to the clot front and aggregated in the interior of the clots than others. These results might be attributed to the positive charges of the CS and the interaction between

RGD and GP IIb/IIIa receptors on the platelet membranes included in the blood clots.

3. Conclusion

A thrombus developed in the circulatory system can cause vascular blockage leading to serious consequences such as arterial and venous thrombosis including myocardial infarction, ischemic stroke, peripheral arterial thrombosis, deep venous thrombosis and pulmonary embolism. These are common and potentially life-threatening vascular diseases. To treat such thrombotic diseases, several plasminogen activators have been developed. However, no single agent has been approved by the US FDA to be labeled for every indication. Thus, for better control of these events, new agents and new dosing regimens are under constant investigation. Current regimens are limited by the failure of initial reperfusion and reocclusion and are associated with an increased risk of bleeding complications. Blood platelet adhesion and aggregation are known to play an essential role in the formation of thrombus during a variety of pathological events such as atherosclerosis or DVT. Hence, these cells have been targeted by another form of targeted clot therapy such as GP IIb/IIIa receptor antagonist. By targeting actual thrombus using ligand–receptor mediated targeting, thrombolysis might be increased with reduced chances of hemorrhage. The platelets integrin receptors are one of these types of receptors which might be a potential site for the improved therapy of thromoembolism.

4. Expert opinion

Thrombolytic drugs play a critical role in the treatment of acute myocardial infarction, pulmonary embolism, DVT, arterial thrombosis and peripheral vascular thromboembolism. Thrombolytic agents which are either approved or under clinical investigation are plasminogen activators like streptokinase, urokinase and t-PA. These agents act by converting plasminogen to the plasmin. However, these agents suffer the problems of high dose, re-occlusion and hemorrhage because of non-specific action. The targeted drug delivery approach has been intensively studied for the improvement of several complicated diseases like cancer. Cell-selective targeting in the area of cardiovascular disease is now a growing area for research. The basic problems with plasminogen activators are less half-life and immunogenicity because of their foreign nature. By encapsulating proteins inside the novel carrier systems, increased half-life and decreased immunogenicity might be obtained. Liposomes have previously been thoroughly studied in the delivery of plasminogen activators. It was found that liposome encapsulation not only increases the half-life but also reduces immunogenicity and increases systemic stability without compromising therapeutic activity. Some of these studies also indicated the localization of these vesicular systems in the thrombus, that is targeting ability of vesicular constructs. However, increase in circulatory half-life also increases other complication due to the system-wide presence of long-lasting, active plasmin, which further increases hemorrhage complications. To reduce such a risk of long-term hemorrhage, targeted delivery might be beneficial. By targeting drugs to the site of thrombus, plasmin activity may be constrained to the site of thrombus, and thus act only in the region of the blood clot.

Integrin receptors are the receptors which are present on the surface of platelets, but in the resting state they have no ligand receptive site for the attachment of fibrinogen. It has already been reported that platelets play a major role in the formation of thrombus by the adhesive and aggregation process using integrin receptors. Furthermore, it was postulated that integrin receptors might be a possibility for the targeted therapy or targeted delivery of thrombolytic agents. Various agents that have affinity towards the GP IIb/IIIa receptor are under clinical studies. If these targeting agents were coupled at the surface of any novel carrier, it may be helpful in the delivery of these carriers to the site of thrombus. To confirm all these speculations, many studies have been performed by attaching these ligands either directly to the active moiety or to the carrier containing the active moiety. Liposomes have been used for the delivery of streptokinase to the site of thrombus, however to further increase the targeting potential of liposomes, it was appended with RGD peptide, a sequence found in the α-chain of the fibrinogen. RGD peptide attached liposomes show specificity towards the platelets that are the active component of the thrombus. Due to stability problems of liposomes, particulate carrier systems have also been studied for the delivery of plasminogen activators.

A new approach for the targeted delivery of thrombolytic agents is based on direct attachment of the targeting motif to the active moiety. In one study GP IIb/IIIa receptor antibody was conjugated with urokinase and found specificity to the thrombus. Further studies are required to develop these novel targeted drug delivery systems in patients suffering from cardiovascular complications. Finally, from a commercial point of view, targeted thrombolytic delivery systems may reduce the cost of therapy by reducing dose and side effects, as well as by increasing the therapeutic benefits. In future, these approaches could be a platform for the delivery of thrombolytic agents for better control of cardiovascular diseases.

Declaration of interest

The authors state no conflict of interest and have received no payment in the preparation of this manuscript.

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