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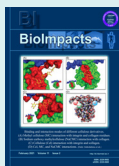


Targeted delivery of thrombolytic enzymes

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Summary

Although thrombolytic agents have been used for several decades in the treatment of thromboembolic conditions, there is an unmet need for the development of safer thrombolytic agents. The development of new molecules themselves may not be sufficient. This has sparked a growing interest in the design of novel nanoscale drug carrier systems for the delivery of thrombolytic enzymes in an effort to address its fatal side effects. There are numerous proof-of-concept reports on such nanoscale systems that seek to capitalize on the pathophysiologic signatures of thrombosis as well as external biochemical/physical triggers. Although there may be a long road ahead before we have such new nanoscale therapeutics on the bedside, hopes remain high.

Author's Biosketch

Young M. Kwon received his Ph.D. from University of Utah (USA) and his postdoctoral training at University of Michigan (USA). He is currently an Associate Professor of Pharmaceutical Sciences at Nova Southeastern University College of Pharmacy (USA). Dr. Kwon's research interests include targeted delivery and controlled release of biological molecules.



One can find in the literature that the impact of nanobiotechnology has been explosive in anticancer drug delivery research during the last two decades or so, but can also feel such impact in research efforts in applying nanoscale drug and gene delivery in several other disease categories for quite some time. Without a doubt, cardiovascular disease is a great area that can be benefited by combining such technologies with novel therapeutic concepts.

Thrombosis can be a hallmark of certain cardiovascular diseases such as myocardial infarction (MI; due to coronary artery thrombosis) and ischemic stroke (IS), which are associated with significant morbidity and mortality.¹ For several thromboembolic conditions, restoration of blood flow by rapid dissolution of the blood clot is a logical therapeutic approach.² Since the 1980s, following streptokinase, recombinant human tissue plasminogen activator (rtPA or tPA; Alteplase) has been a dominant thrombolytic agent in clinics while a number of variant forms of plasminogen activators (PAs) have been tried.²

Blood clot (i.e., thrombus) mainly consists of fibrin (Factor 1a), where erythrocytes and platelets are entrapped. Fibrinolysis is an important part of hemostasis

and is initiated by activation of circulating plasminogen, a catalytically inactive zymogen, by a PA. Streptokinase, a first-generation thrombolytic, is of bacterial origin and binds to circulating plasminogen. Contrary to what the name may imply, there is no enzymatic cleavage of the substrate (plasminogen) and the complex itself possesses fibrinolytic activity, caused by a conformation change in plasminogen via streptokinase binding.³ On the other hand, tPA and its analogs catalytically convert plasminogen into plasmin, an active fibrinolytic enzyme. In addition, tPA is a fibrin-specific agent, meaning that its activity increases by orders of magnitude when bound to the surface of a fibrin clot.³

Thrombolytic agents, due to their molecular sizes, must be administered directly into the blood via an intravascular route, generating systemic effects and a lytic state. Unlike the usual amount of tPA that a normal body sees, a huge dose (0.9 mg/kg for IS, not to exceed 90 mg (100 mg for MI)) is given partly because tPA is degraded so quickly upon administration. Its blood residence is only a matter of minutes, although that of the newer variant (Tenecteplase, TNKase[®]) is somewhat extended.² The very mechanism of thrombolysis via PA can also



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lead to serious bleeding complications due to the rapid enzymatic consumption of key clotting factors (such as fibrinogen, Factor I).⁴ Thrombolytic agents are drugs with deleterious side effects. Therefore, the approaches utilizing nanocarrier/ targeted delivery are highly justified.

The idea of targeted thrombolysis goes back nearly three decades. Dewerchin and coworkers designed a bioconjugate consisting of an antiplatelet antibody and a single-chain urokinase (sc-uPA) to demonstrate a proof-of-concept (in terms of clot lysis and bleeding time) in a rodent model.⁵ In the late 1990s, Yang and coworkers developed a two-part system composed of charge-modified anti-fibrin antibody and tPA joined via electrostatic interactions that can be undone by protamine, a basic peptide, and a clinical heparin antidote.^{6,7} Later, a platelet targeted, electrostatic nanocomplex triggered by a therapeutic dose of heparin was designed⁸, using the 14-mer peptide sequence from the gamma-chain of fibrinogen, which has a high affinity toward activated platelet surface (glycoprotein IIb/IIIa).^{8,9} An endogenous trigger was also incorporated in a prodrug type of tPA that can be activated by the presence of a thrombin gradient near thrombus.¹⁰ In addition, there has been a steadily growing interest in seeking a particulate type of nanocarriers combined with targeting and release mechanisms in the delivery of thrombolytic agents during the past decade. Vyas and coworkers designed a liposomal carrier with RGD peptide on the surface of the liposomes to deliver streptokinase triggered by shear forces on the clot.^{11,12} Ultrasound triggered nanosystems appears to be promising: a cationized gelatin/tPA complex^{13,14} and microbubbles.¹⁵ Last but not least, superparamagnetic nanoparticles are also featured in targeted delivery of thrombolytics.¹⁶

Yet, the list of examples mentioned above is only partial; for a more detailed introduction of thrombolytic agents and nanocarrier approaches for thrombolytics, readers are directed to recent, comprehensive reviews by Hassanpour and coworkers¹⁷ and Zenych and coworkers.¹⁸ There certainly is a growing and/or renewed interest in this area. However, these systems, like other targeted nanosystems, tends to be complex. Hopefully, some of these systems overcome hurdles of further development as viable pharmaceutical products and contribute to better treatment outcomes in thromboembolic diseases in the near future.

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Ethical statement

Not applicable.

Competing interests

None declared.

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