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Review

Mimicking the fibrinolytic system on material surfaces

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ABSTRACT

Clotting and thrombosis remain the most serious problems in the development of blood contacting devices such as heart valves, vascular stents, grafts and catheters. No material exists that does not provoke these phenomena and coagulation appears to be inevitable when a foreign (i.e. non-endothelial) surface is in contact with blood. As an alternative to a surface that prevents coagulation, the concept of a clot-lysing or fibrinolytic surface is attractive. By designing the surface effectively to mimic the fibrinolytic system in the vasculature, it may be possible for clots to be lysed (effectively dissolved) as they form. In this review we elaborate on this concept and discuss ways in which such a surface could be realized. Developments in this area to the present time are reviewed, and some perspectives for future research are presented.

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Contents

1. Introduction

Despite advances in blood-contacting biomaterials for clinical applications, the problem of foreign surface induced thrombosis remains unsolved. For example, the long-term performance of grafts of diameter less than 6 mm is still far from satisfactory. Polytetrafluoroethylene (PTFE)-based grafts perform well for above-knee femoropopliteal bypass up to 2 years, beyond which patency rates fall below those of saphenous vein grafts [1,2] due predominantly to thrombosis. Coronary artery stents including drug-eluting stents (DES) are also subject to thrombotic complications. It was reported by Luscher et al. that while DES showed restenosis rates below 10%, late stent thrombosis (3 years after implantation and beyond) was observed in a number of patients [3].

A variety of approaches to anti-thrombogenic surfaces have been pursued [4,5]. Examples include materials modified with bioinert polymers such as polyethylene oxide (PEO) and various zwitterionic polymers (found to be highly resistant to nonspecific protein adsorption when used as surface modifiers [6,7]); materials with incorporated anticoagulants, notably heparin; materials having a porous surface texture to encourage limited thrombosis that can re-organize to a pseudo-endothelium. These and other approaches have so far met with only limited success. They are in general based on the idea of preventing clot formation; this has so far proved to be impossible.

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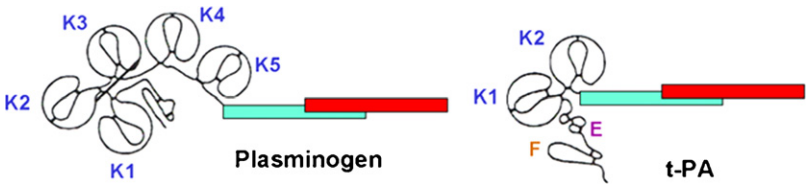

Fig. 1. Modular structure of plasminogen and t-PA. K: kringle; F: finger domain; E: epidermal growth factor; red line: serine proteinase domain. Reproduced from [8] with permission (Elsevier Science Ireland Ltd.). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

While coagulation appears to be inevitable when a foreign (i.e. non-endothelial) surface is in contact with blood, one may consider whether a surface could be designed to lyse the clot before it poses a danger to the patient. A possible way to realize this concept is to design the surface to adsorb preferentially from blood the essential components of the fibrinolytic system, namely plasminogen, the precursor of the clot lysing enzyme plasmin, and a plasminogen activator (e.g. tissue plasminogen activator, t-PA). Such a surface would mimic the naturally occurring fibrinolytic process that occurs on the surface of fibrin [8]. This concept has been pursued in our laboratories over the past several years [9–21]. The present contribution is intended, in part, as an elaboration of this concept and an outline of developments to date.

The related concept of a t-PA releasing surface has also been suggested but has not been developed to any significant extent for blood contacting material applications. In contrast to the clot lysing surface described above, however, where fibrinolytic activity is localized to the surface, a t-PA releasing surface initiates lysis by delivering t-PA to the clot in the bulk blood for generation of plasmin. Recent literature in this area is also reviewed.

It is our hope that this brief resumé and review may serve to stimulate additional research on this neglected, but promising and potentially important, approach to blood compatibility.

2. Fibrinolytic surface: the concept

The normal hemostatic process involves fibrinolysis as well as fibrinogenesis. Formation of fibrin in haemostasis is part of the physiological response to vascular injury; fibrinolysis effectively removes fibrin by proteolytic degradation once the injury is repaired. Vascular patency is thus maintained.

Plasminogen, the central protein of the fibrinolytic system, is secreted primarily from hepatocytes into circulating blood and body fluids. It is a 94 kDa protein that contains 5 kringle domains, two of which (K1 and K4) provide lysine binding sites (LBS) that bind with high affinity to carboxy-terminal lysine residues of progressively degraded fibrin [22] (Fig. 1).

Activation of plasminogen to plasmin results from cleavage of the Arg_{561}-Val_{562} peptide bond, exposing the serine protease domain in the carboxy-terminal region (Val_{562}-Asn_{791}) that degrades fibrin to small fragments referred to as fibrin degradation products (FDP). t-PA is the primary physiologic activator of plasminogen. It is a protein of molecular weight 65 kDa and circulates in the blood at a concentration of about 6 μg/L. The concentration is maintained at a low value due to enzymatic digestion and the action of inhibitors resulting in a circulating half-life of ~5 min. It is released from damaged endothelial cells when a blood vessel is injured, and this ensures vascular patency after wound healing. t-PA can bind to fibrin through a high affinity LBS in one of its two kringle regions and a second non-lysine-dependent binding site within its finger domain (Fig. 1). During the fibrinolysis process, fibrin functions as a suicide cofactor that binds plasminogen and t-PA, forming a three-way complex with catalytic advantages. The rate of activation of plasminogen in this ternary complex (K_m = 20–200 nM) is much higher than in the absence of fibrin (K_m = 63 μM) [23]. In the circulating blood, inhibition of fibrinolysis may occur at two levels: inhibition of plasmin by endogenous α_2-antiplasmin and inhibition of t-PA by plasminogen activator inhibitor-1 (PAI-1). However, neither of these inhibitors can act on fibrin-bound plasmin or t-PA. Solid phase activation and fluid phase inhibition thus ensure the specificity of fibrinolysis and control the extent of fibrin degradation [8].

Inspired by the physiologic mechanism of fibrinolysis, one may set out to design a surface that can lyse fibrin which begins to form on it. A first and major requirement is that the surface in contact with blood should adsorb plasminogen in significant quantity. It has been reported that a carboxy-terminal lysine residue is an essential element for localization of plasminogen on fibrin or cell surfaces [22]. Therefore, lysine may serve as an affinity ligand for plasminogen binding in the construction of a fibrinolytic surface. In fact, as early as 1970, Deutsch and Mertz exploited the strong affinity of plasminogen for lysine in the development of a convenient affinity chromatography method (lysine-sepharose column) for the purification of plasminogen [24]. A second major requirement is that the adsorbed plasminogen should be activatable to plasmin, i.e. t-PA or other activator should be present. As indicated, t-PA also has a high affinity kringle-type lysine binding site, so in principle a surface containing lysine residues should also be able to bind t-PA in contact with blood. Thus it seems possible that a lysine-containing surface in contact with blood should be able to lyse fibrin by specifically binding plasminogen and its activator to generate plasmin. The hypothesized clot lysing process on a lysine containing surface is shown in Fig. 2.

3. Fibrinolytic surface with directly immobilized lysine

Brash and coworkers first suggested the concept of a fibrinolytic surface based on the capture of plasminogen by immobilized lysine. In initial work, the adsorption of plasminogen from buffer or plasma to lysine-containing polyurethanes (PU) was investigated [9,10]. Lysine was attached through sulfonate groups on the PU chains. It was found that although plasminogen was adsorbed extensively on the lysine containing surfaces, control surfaces without lysine showed similar binding capacity.

Analogous silica glass materials (containing sulfonate groups and lysine residues) with potentially greater capacity for lysine immobilization were also investigated [11–13]. Estimates of the

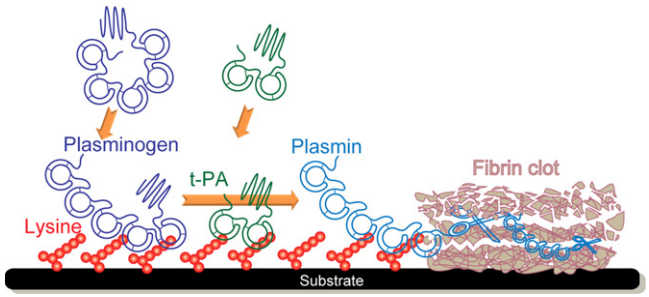

Fig. 2. Schematic representation of the lysine-based clot lysing surface.

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