Immunobiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Immunobiology

journal homepage: www.elsevier.com/locate/imbio

Complement-coagulation crosstalk on cellular and artificial surfaces

Rebecca Wiegner, Shinjini Chakraborty, Markus Huber-Lang*

Department of Orthopedic Trauma, Hand-, Plastic- and Reconstructive Surgery, University Hospital of Ulm, Germany

ARTICLE INFO

Article history:
Received 16 April 2016
Received in revised form 2 June 2016
Accepted 9 June 2016
Available online xxx

Keywords:
Complement
Coagulation
Crosstalk
Cellular surfaces
Artificial surfaces

ABSTRACT

The humoral serine proteases of the complement system and the coagulation system play central roles during the events of an inflammatory response. While the complement system confers immunoprotective and -regulatory functions, the coagulation cascade is responsible to ensure hemostatic maintenance. Although these two systems individually unfold during inflammation, several studies have reported on the "crosstalk" between components of the complement and the coagulation system in the fluid phase. However, both cascades are usually initiated on or in close proximity to foreign or activated surfaces, and there is increasing evidence for interacting complement and coagulation proteins on various superficial areas on endothelium, circulating entities like platelets, leukocytes, microparticles and pathogens, and even on artificial surfaces. This review aims at summarizing these interactions to complete the picture.

Contents

1. Introduction

The complement and the coagulation system are two evolutionarily ancient cascades, consisting mainly of trypsin-like serine proteases and their activators as well as inhibitors, that are indispensable in the recognition and sealing of injured tissue, preventing further blood loss and development of infection.

Complement is activated *via* three different pathways (the lectin, classical or alternative pathway) and results in cleavage of complement factors, leading to the opsonization of pathogens and activation and recruitment of immune cells in order to migrate to the site of injury. In the following, complement activation products lead to secretion of proinflammatory mediators, ingestion of opsonized particles by various immune cells, and the direct lysis of pathogens by pore formation (Merle et al., 2015a, 2015b).

Coagulation activation on the other hand can occur through the extrinsic pathway, which is considered to be of high relevance *in vivo*, or the intrinsic (contact activation) pathway that seems to be rather related to inflammatory processes (Davie and Ratnoff, 1964; Adams and Bird, 2009). Both pathways result in activation of factor (F) X and prothrombin, and subsequent fibrin polymers forming a clot together with activated platelets. The resulting thrombus can later be resolved by the fibrinolytic cascade through the generation of plasmin (Oikonomopoulou et al., 2012).

Earlier considered to be two structurally similar but separate systems, evidence has accumulated for close interactions between complement and coagulation since the observation that blood withdrawal without anti-coagulant additives, apart from coagu-

* Corresponding author.
E-mail address: markus.huber-lang@uniklinik-ulm.de (M. Huber-Lang).

http://dx.doi.org/10.1016/j.imbio.2016.06.005
0171-2985/

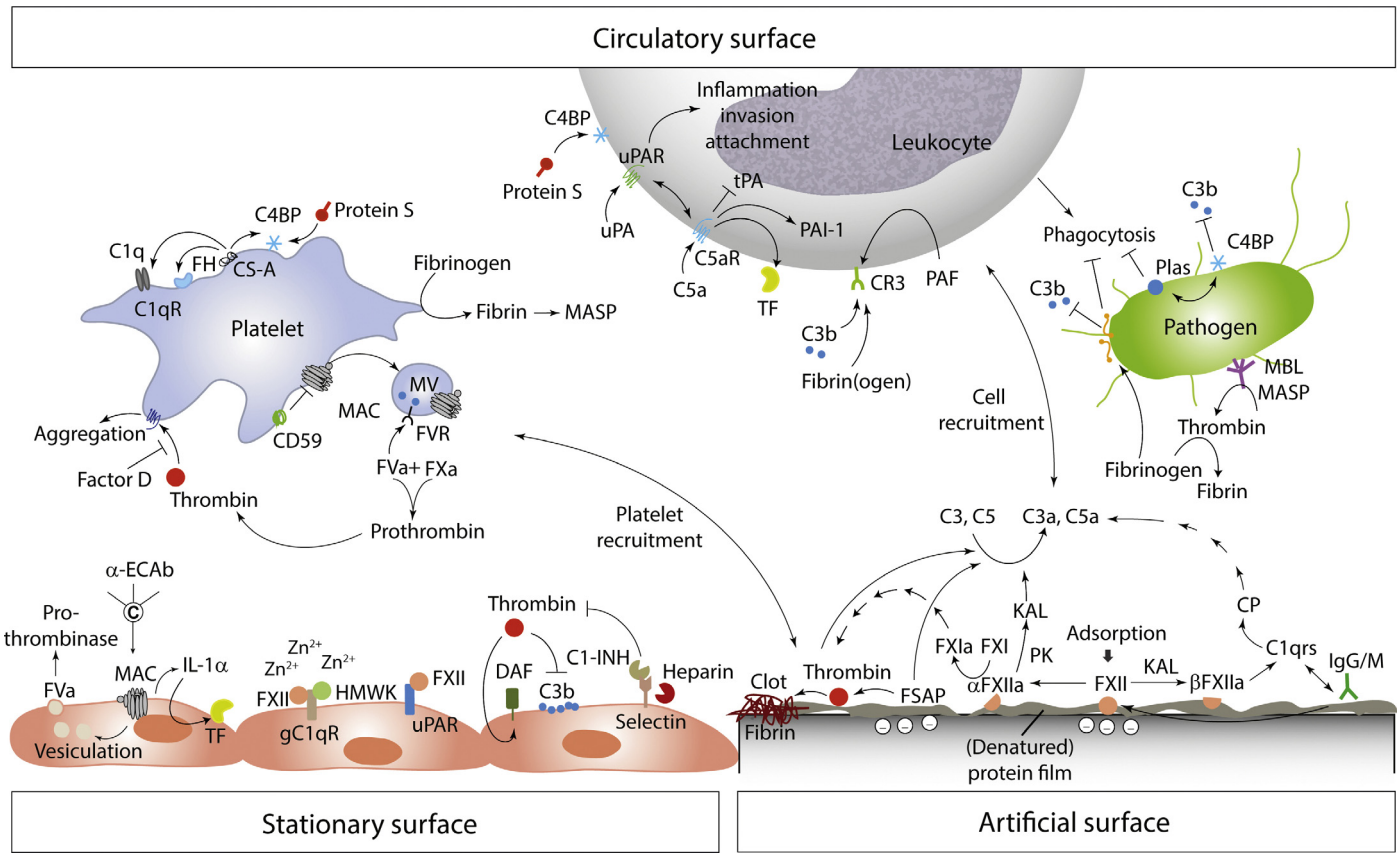

Fig. 1. Complement and coagulation can interact on stationary, artificial and circulating surfaces. On stationary surfaces such as endothelial cells, complement activation and MAC generation on the membrane can induce the secretion of vesicles and the formation of a prothrombinase complex or, *via* secretion of IL-1α, the expression of tissue factor. FXII and HMWK bind to endothelial gC1qR in the presence of Zn^{2+}. Thrombin induces DAF expression on endothelial cells, thereby preventing C3b surface deposition, which can be inhibited by selectin-bound C1-INH in a heparin-dependent manner. Entities such as platelets, microvesicles, leukocytes and pathogens provide circulating platforms for interactions between complement and coagulation. On activated platelets, surface exposure of CS-A or the presence of protein S contributes to binding of C1q, C4BP and FH. Fibrinogen cleaved by platelets leads to activation of MASPs. MAC membrane formation, prevented by platelet CD59 expression, can trigger shedding of microvesicles rich in FVaR that initiate prothrombinase formation. Similarly to platelets, protein S increases localization of C4BP on leukocyte surfaces. The cellular receptor of uPA, uPAR, as a mediator of inflammation, invasion and attachment also regulates C5aR signaling; *vice versa*, C5a stimulus upregulates uPAR expression. Furthermore, it induces a change from pro-fibrinolytic tPA to anti-fibrinolytic PAI-1 as well as the production and secretion of TF. PAF can prime cells to closer interaction with C3b-opsonized particles *via* CR3 or binding to fibrin(ogen). Pathogens utilize several crosstalk mechanisms to evade recognition and clearance by innate immunity. Thrombin activation by MASPs induces fibrinogen turnover. Recruitment of C4BP, fibrin(ogen) and plasminogen to the bacterial surface prevents C3b deposition and phagocytosis. Interactions between complement and coagulation also take place on artificial surfaces after adherence of intact or denatured proteins. Adsorption of FXII as a sensor of negatively charged structures initiates auto-cleavage which leads, directly by activation of prekallikrein or indirectly *via* induction of the classical pathway, to the cleavage of C3 and C5. FSAP with a high affinity for negatively charged polymers and thrombin are also capable of cleaving C3 and C5. IgG-IgM complexes can synchronously trigger complement activation and FXII pro-coagulant activity, thereby increasing recruitment of platelets and proinflammatory processes. See text for more details. Abbreviations: α-ECAb, anti-endothelial cell antibody; C1q/3/4b/5, complement component 1q/3/4b/5; C1-INH, C1 inhibitor; C1qR, C1q receptor; C4BP, C4b-binding protein; C5aR, C5a receptor, CP, classical pathway; CR3, complement receptor type 3; CS-A, chondroitin sulfate A; DAF, decay-accelerating factor; FH, complement factor H; FSAP, factor VII-activating protease; FVa, activated coagulation factor V; FVR, factor V receptor; FXa, activated coagulation factor X, FXII, coagulation factor XII; α/β FXIIa, alpha/beta-coagulation factor XII; HMWK, high molecular weight kininogen; KAL, kallikrein; MAC, membrane attack complex; MASP, mannose-binding lectin-associated serine protease; MBL, mannose-binding lectin; MV, microvesicle; PAI-1, plasminogen activator inhibitor-1; PAF, platelet-activating factor; Plas, plasminogen; PK, prekallikrein; TF, tissue factor; tPA, tissue plasminogen activator; uPA, urokinase; uPAR, urokinase receptor.

lation, also strongly induces activation of the complement system (Mollnes et al., 1988). Several studies have demonstrated that active components of the coagulation cascade can cleave and/or activate proteins of the complement system (Amara et al., 2010; Huber-Lang et al., 2006; Kanse et al., 2012) and *vice versa* (Gulla et al., 2010; Krarup et al., 2007) as comprehensively reviewed elsewhere (Oikonomopoulou et al., 2012; Markiewski et al., 2007). Most of the described interactions take place in the circulation and on a fluid level. However, due to the fact that both systems require contact with surfaces for initiation, one might miss a substantial part of the picture focusing only on the fluid phase. We therefore aimed to summarize the current knowledge on how interactions on stationary and circulating as well as artificial surfaces can influence activation and regulation of the coagulation and complement system. The interactions described herein are shown in Fig. 1.

2. Crosstalk on stationary cell surfaces

The endothelium is a classic example of a stationary cell layer which has been proposed as a potential surface for complement-coagulation crosstalk. The local resolution of an infection during inflammatory responses is characterized by an activated endothelium. While several interactions between the two protease cascades in the fluid phase have been previously reported, the function of various complement and coagulation proteins have only been separately elucidated on the endothelial surface (Karpman et al., 2015; van Hinsbergh, 2012). Earlier studies mainly indicated an indirect complement-coagulation cross-talk. Heparan sulphate proteoglycan (HSPG) was identified as a potent anticoagulant expressed on endothelial cells (Marcum et al., 1986), which was released from the cell surface upon C5a stimulus (Platt et al., 1991). An anticoagulant activity was seen to be mediated by HSPG uptake of FXa and