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Review

Cross-talk between the complement and the kinin system in vascular permeability

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ABSTRACT

The endothelium is a continuous physical barrier that regulates coagulation and selective passage of soluble molecules and circulating cells through the vessel wall into the tissue. Due to its anatomic localization, the endothelium may establish contact with components of the complement, the kinin and the coagulation systems which are the main, though not exclusive, inducers of vascular leakage. Although the complement and the kinin systems may act independently, increasing evidence suggest that there is a crosstalk that involve different components of both systems. Activation is required for the function of the two systems which are involved in pathological conditions such as hereditary and acquired angioedema (AE) and vasculitidis. The aim of this review is to discuss the contribution of complement and kinin systems to vascular leakage and the cross-talk between the two systems in the development of AE. This clinical condition is characterized by episodic and recurrent local edema of subcutaneous and submucosal tissues and is due to inherited or acquired C1-INH deficiency. Although the pathogenesis of the swelling in patients with AE was originally thought to be mediated by C2, ample evidence indicate bradykinin (BK) as the most effective mediator even though the possibility that both the complement and the kinin-forming systems may contribute to the edema has not been completely excluded. BK induces endothelial leakage interacting with B2 receptors but other molecules may be involved in the onset and maintenance of AE. In this review we shall discuss the role of B1 receptors and gC1qR/p33 in addition to that of B2 receptors in the onset of AE attacks and the importance of these receptors as new possible molecular targets for therapy.

1. Introduction

The vascular tree is covered on the inner surface by a continuous layer of endothelial cells which form a physical barrier between the circulating blood and the extravascular tissue preventing potential damage which may derive from undesired blood outflow. Besides playing a critical role in physically separating the intravascular from the extravascular sides of the vascular vessels, the endothelium exhibits other important functions to maintain vascular homeostasis. By expressing heparin sulphate, and by releasing thrombomodulin and tissue factor inhibitor, endothelial cells (ECs) expose an anti-thrombotic surface on the luminal side which controls blood flow preventing blood clot. The endothelium can also regulate the vascular tone contributing to induce changes in the blood flow in response to tissue demands. Several substance can be released by ECs which either promote vasodilation, such as nitric oxide and prostacyclin PGI2, or induce vasoconstriction, as is the case of endothelin-1 and platelet-activating factor [1].

Another important function of the endothelium is to control passage of molecules and cells to the extravascular sites where they are needed for nutritional and defence purposes. This is made possible by its structural organization as a monolayer of cells joined together by tight junctions, a structure observed in the microcirculation of almost all tissues and organs with only a few exceptions.

Perturbation of ECs caused by physicochemical stimuli induces cell activation and has functional consequences resulting in cell egression into the extravascular sites and increased vascular permeability. These changes are usually associated with inflammatory processes which are responsible for systemic manifestations, such as sepsis or generalized vasculitides, or localized reactions. However, vascular leakage which manifests as non inflammatory edema may also occur in some pathological conditions in the absence of inflammation.

The soluble systems which are mainly, though not exclusively, involved in the induction of increased vascular permeability include the complement (C) and the kinin systems, which may have a direct permeabilizing effect through the release of biologically

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active products or may activate other cells which in turn release vasoactive molecules. Although the two systems may act independently to induce vascular leakage, increasing evidence suggests that there is a cross-talk which involves different components of these systems. Both systems require activation to function and are involved in triggering or exacerbating pathological conditions such as hereditary and acquired AE and vasculitidis.

The focus of this review is to discuss the contribution of C and kinin systems to vascular leakage and to highlight the cross-talk between the two systems in the development of AE.

2. Contribution of the complement system to the vascular leakage

The C system is an important component of innate immunity involved in host defence against microorganisms, clearance of immune complexes and removal of apoptotic cells and acts either alone or more often in collaboration with other components of both innate and acquired immune system. To accomplish these functions, the system must be activated to release biologically active products which may directly neutralize the target or favour the participation of other components of the immune system to complete the protective action. Complement activation may occur on the cell membrane and/or in the fluid phase and shares with the activation of the kinin system the characteristic feature to proceed in a cascade fashion leading to the release of a progressively increased number of biologically active products. These products are formed at various steps of the C sequence initiated by different components which trigger distinct activation pathways.

ECs are continuously exposed to C components present in circulating blood or at extravascular sites and establish with the C system multiple interactions which have important functional consequences. To begin with, the endothelium is an important source of C components and regulators at tissue level [2] and together with macrophages, fibroblasts, and several other cell types, contributes to the pool of circulating plasma components which are not synthesized in the liver as is the case of C7 [3]. This terminal C component is not only secreted by ECs but also expressed on the cell surface as a means of protection against the damaging effect of SC5b-9 [4]. On the other hand, ECs represent a potential target of biologically active products which are formed as a result of C activation on the cell surface or in the fluid phase. Complement-fixing antibodies reacting with antigens expressed or bound to ECs can bind C1q and trigger the C sequence through the classical pathway. These antibodies can be found in patients with autoimmune diseases associated with vasculitides and in patients undergoing hyperacute graft rejection. Anti-phospholipid antibodies interacting with β2GPI which binds to receptors expressed on ECs represent another example of C-fixing antibodies [5,6]. The lectin pathway can also be activated on cultured ECs exposed to oxidative stress [7] which leads to the exposure of sugar moieties – such as mannose, fucose or N-acetylglucosamine – usually expressed on the surface of bacterial pathogens or altered cells [8]. MBL binding and C activation through the lectin pathway has also been documented *in vivo* on rat myocardium [9] and mouse kidney [10] undergoing ischemia-reperfusion injury.

Although the two pathways use different components in the early phase of the activation sequences including C1r and C1s, for the classical pathway, and MASPs, for the lectin pathway, they share C4 and C2 to form the C3 convertase which in turn activates C3 resulting in the split of this molecule into C3a and C3b [11].

Isolated C1q can interact with ECs by directly binding to receptors which recognize the collagen portion (cC1qR) [12] or the globular head (gC1qR) [13]. Since C1q tends to form a loose complex with C1r and C1s in both plasma and extravascular fluids, free C1q is made available mostly after activation of the classical pathway which results in the release of C1q from the complex following the dissociation of C1r and C1s by C1 inhibitor. Binding of C1q to C1qR stimulates ECs to express adhesion molecules [14] and to release the chemotactic factors IL-8, MCP-1 and IL-6 [15]. However, evidence that C1q may also promote EC leakage is lacking. C1s is the only early component which was previously shown to induce vascular permeability following intradermal injection into guinea pig [16]. This effect was later attributed to a split product of C2 generated by activated C1s [17]. However, subsequent studies failed to identify a C2-derived fragment with these properties [18].

Cleavage of C3 and C5 by the C3 and C5 convertases respectively results in the release of the small peptides C3a and C5a which interact with receptors expressed on ECs [19,20]. Both C3a and C5a induce cytoskeletal changes on ECs [21] and up-regulate IL-8, IL-1β and RANTES mRNA [20], but the two anaphylatoxins differ because C5a causes a decrease in IL-6 mRNA [20] and is chemotactic for dermal microvascular ECs [21].

Intradermal injection of C3a purified from an inflammatory exudate into rat skin was reported to enhance vascular permeability [22]. The involvement of C3 in vascular leakage was also confirmed in an *in vivo* model of immune complex-mediated disease in mice, as indicated by the marked decrease in the vascular permeability induced by immune complexes in C3 depleted mice [23]. C3a is likely to exert an indirect effect on vascular leakage since purified C3a fails to cause permeability of the EC monolayer [21]. This is in contrast with the ability of C5a to cause cell retraction, gap formation and consequent permeability of ECs evaluated by FITC-dextran passage [21].

The fragment C5a is released in inflammatory conditions associated with bacterial infections. A typical example is the infection caused by *Aeromonas sobria* which cleaves C5 through a serine protease with the release of C5a which induce histamine-mediated vascular leakage [24].

More recently, the potential role of C5aR in endotoxin-induced plasma leakage was documented in a mouse model following the observation that the administration of C5aR–siRNA was effective in preventing endothelial injury and vascular leakage [25].

Activation of ECs is also induced by the late C components from C5 to C9 involved in the assembly of the terminal C complex (TCC). The formation of this complex is initiated with the release of C5b from cleaved C5 (Fig. 1), followed by progressive binding of the remaining late C components from C6 to C9 (Fig. 1). This complex may cause cytolysis through a pore formation following insertion into the plasma membrane of target cells [26], or as a sublytic complex which fails to cause cell lysis despite its binding to the phospholipids bilayer of the cell membrane. The TCC can also assemble in the fluid phase where it accumulates as a cytolytically inactive complex due to the short half-life of its cell binding ability. The complex binds the soluble C regulators S protein and clusterin and circulates in plasma or is present in the extravascular fluid as SC5b-9 [27]. We have shown that this complex, despite its inability to cause cytolysis, promotes vascular leakage [27]. This effect was documented *in vitro* using a transwell system to evaluate the leakage of fluorescein-labeled BSA or the intravital microscopy to follow the extravasation of circulating FITC-BSA across mesenteric microvessels [27]. The permeabilizing activity of SC5b-9 was partially inhibited by the B2R antagonist (HOE-140), or the selective platelet activating factor (PAF) receptor antagonist (CV3988) and was completely neutralized by the mixture of the two antagonists suggesting that the effect of SC5b-9 is mediated by the formation of BK and the release of PAF.

Our observation was further supported by the finding of high levels of SC5b-9 in pleural fluids of patients affected by Dengue virus infections [28]. In these patients, who die mainly from vascular leakage and shock, the nonstructural viral protein 1 (NS1)