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Review Article

Cooperation between Complement and Kinin Systems in Angioedema Episodes

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Abstract

Angioneurotic edema is characterized by an undesirable and localized increase in vascular permeability. The endothelium is a continuous physical barrier that regulates selective passage of soluble molecules through the vessel wall into the tissue. Due to its anatomic localization, the endothelium may contact components of the complement, the kinin and the coagulation systems.

The complement system, one of the major components of innate immunity, elicits an important function in the vascular leakage modulating the release of kinins. During the angioedema attacks a complex interplay is established among the endothelium, the complement proteins or its activation products, and the kinin system leading to the pathogenic effects of the disease.

The involvement of B1-Receptors and gC1qR/p33 besides B2-Receptors in the onset of angioedema attacks must be further investigated and their importance as new possible molecular targets for therapy should be considered.

Keywords: Angioedema; Complement; Endothelium; Kinins; C1-Inhibitor; gC1qR/p33

Abbreviations

AE: Angioedema; BK: Bradykinin; C: Complement; B1R: Bradykinin Receptor 1; B2R: Bradykinin Receptor 2; EC: Endothelial Cell; SC5b-9: Cytolytically Inactive Terminal Complement Complex; APL: Attack Phase Plasma; RPL: Remission Phase Plasma; C1-INH: C1 Inhibitor

Introduction

An undesirable increase in vascular permeability has been implicated in various pathological conditions including inflammation, trauma, sepsis, ischaemia-reperfusion, diabetes, atherosclerosis, tumor development and progression and angioneurotic edema (AE). The patients affected by AE disease are subject to recurrent episodes of circumscribed swelling of the skin, intestine, and airway. When the swelling occurs in the intestine, it causes severe abdominal pain, reminiscent of appendicitis, and intestinal obstructions. When the colon is affected, severe watery diarrhea may occur. Swelling in the larynx is the most dangerous symptom, as the affected individual may suffocate to death. Such episodes may be triggered by trauma, menstrual periods, excessive exercise, exposure to extremes of temperature or mental stress, but the majority of the attacks remain apparently spontaneous [1-3].

While several key systems may be activated during AE attacks, the contact system, the factor XII–dependent fibrinolytic cascade and the complement system seem to be the most important factors involved in the disease [4]. While many mediators, e.g. bradykinin (BK), thrombin, histamine and vascular endothelial growth factor, disrupt inter endothelial junctions and integrin-extracellular matrix complexes to promote unrestricted vascular leakage, BK is considered the key mediator of AE episodes [5]. The aim of this review is to increase the understanding of the factors promoting AE development. In particular we will analyse the involvement of B1-Receptors (B1R) and gC1qR/p33 besides B2-Receptors (B2R) in the onset of AE attacks.

Furthermore we will focus on their importance as new possible molecular targets for therapy.

The complement system

The complement system is one of the major components of innate immunity which is involved in host defence against microorganisms acting either alone or in collaboration with other components of both innate and acquired immune system. Many other important functions are played by that system, in particular it acts in the clearance of immune complexes and apoptotic cells and in the triggering of the local inflammatory processes through the release of activation products. The system is composed by more than 35 proteins either soluble in plasma or associated with cell membranes [6]. The plasma complement components are mainly produced by the liver although macrophages, fibroblasts, endothelial cells (ECs) and other cells can contribute to their production at the extravascular sites [7].

The activation of the complement system (Figure 1) can take place in the blood stream or at tissue level and it can occurs through three possible activation pathways. The classical pathway is activated by immunocomplexes or other activating factors, recognized by C1q, which is normally present in the blood associated with the serine protease C1r and C1s forming the C1 complex. The lectin pathway is triggered by the mannan-binding lectin (MBL) or ficolins which recognize mannose, fucose or N-acetylglucosamine on the bacterial pathogens surface [6]. From a structural point of view MBL resemble C1q being normally associated in the blood with the MBL associated serine protease (MASPs). These activation pathways share C4 and C2, which are utilized to form the C3 convertase (C4b2b). The alternative pathway is due to a spontaneous activation of C3 which leads to the assembly of a C3-convertase (C3bBb) after the interaction with various cellular surfaces including pathogenic bacteria, parasites, viruses, virus-infected cells and fungi [6]. This pathway acts also as an amplification loop to the other two pathways that generate C3b.

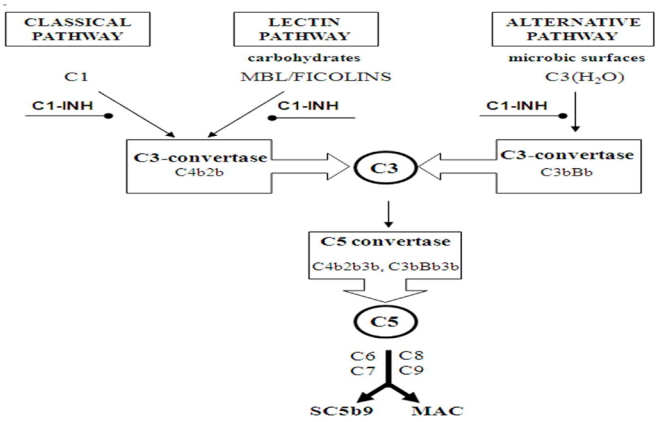

Figure 1. The complement cascade. Classical, alternative and lectin pathways are regulated by C1-INH. It inhibits the enzymatic activity of C1r and C1s in the classical pathway, it blocks the MASPs in the lectin pathway, and it binds to C3b in the alternative pathway, interfering with the formation of the C3 convertase.

The binding of an additional molecule of C3b to the C3-convertases (C4b2b, C3bBb) leads to the formation of C5 convertases (C4b2b3b, C3bBb3b) starting the common terminal part of the cascade (Figure 1). The cleavage of C5 and the activation of the late components of the complement system from C6 to C9 represents the final step of all three pathways and leads to the assembly of the terminal complement complex (TCC). This complex may act as membrane attack complex (MAC), causing cytolysis by insertion into the target cell plasma membrane forming a pore [8], or as a sublytic complex binding to the phospholipids bilayer of the target cells without causing cell lysis. Alternatively, TCC can assemble in the fluid phase, binds to soluble complement regulators such as S protein and clusterin and circulates in plasma or accumulates in the extravascular fluids as a cytolytically inactive complex (SC5b-9) [9].

The biologically active products of the C system may interact with ECs inducing several important functional responses.

Complement regulators

The protection of self cells from the autologous complement attack is ensured by the combined action of fluid phase and cell surface regulatory proteins. Membrane proteins which can control complement activation on cell surface at different steps are represented by complement receptor 1 (CR1; CD35), membrane cofactor protein (MCP; CD46), decay accelerating factor (DAF; CD55) and protectin (CD59). The soluble regulators are present in human plasma but also in body fluids such as in the synovia and in the vitreous humour and regulate the key steps of initiation, amplification and membrane attack of the complement cascade. The soluble regulators include C1-inhibitor (C1-INH), C4b-binding protein (C4BP), factor H, factor I, properdin, clusterin and S protein/vitronectin.

C1-INH is the regulator of the initial step in the C cascade which interacts with the target proteinases C1r and C1s [10]. C1-INH can also inactivate MASP-2 and can regulate the alternative pathway by a reversible binding to C3b [11]. C4BP accelerates decay of C3 convertase.

Factor I cleaves C3b/C4b causing degradation of this molecule in the presence of cofactor proteins, such as the MCP, Factor H or CR1 and C4BP. DAF accelerates the decay of the C3/C5 convertases, while properdin stabilizes the C3 convertase of the alternative pathway. The lytic activity of MAC is regulated in the fluid phase by S protein/vitronectin and clusterin and, on the cell membrane, by CD59 which neutralizes the cytolytic activity of the complex inhibiting the polymerization of C9 within the membrane attack complex [12].

Complement products induce endothelial permeability

ECs represent an heterogeneous population of cells that cover the interior surface of blood vessels. They form a continuous barrier which controls the selective passage of molecules and cells which have to be recruited at the extravascular sites. The endothelium has the ability to prevent blood clotting because of its antithrombotic surface that is kept by heparin sulphate present in the matrix surrounding the cells, by the expression of thrombomodulin and tissue factor inhibitor, and the production of tissue-type plasminogen activator that promotes fibrinolysis. Another important function of the endothelium is to regulate the vascular tone by releasing substances like nitric oxide and prostacyclin PGI2, that promote vasodilation, and others, such as endothelin-1 and platelet-activating factor, that induce vasoconstriction [13].

The activation of the complement system which occurs in the fluid phase or at tissue level induces the release of activation products which can modulate the EC function. These products are sensed by cell surface receptors expressed by the endothelium.

Recently it has been shown the potential role of C5aR in the increase of vascular permeability after LPS stimulation in a mouse model [14].

We have shown that the cytolitically inactive terminal complement complex (SC5b-9) contributes to increase vascular permeability using both in vitro and in vivo models [9]. The in vitro experiments using a transwell model system revealed that the permeabilizing effect induced by SC5b-9 was partially inhibited by the B2R antagonist (HOE-140), or the selective platelet activating factor (PAF) receptor antagonist (CV3988). The addition of the mixture of the two antagonists completely blocked the permeabilizing effect of SC5b-9. These data demonstrate that the increase of endothelial permeability induced by SC5b-9 is mediated by the formation of BK and the release of PAF. The in vitro data were confirmed in vivo monitoring the leakage of FITC-BSA through the mesenteric microvessels by intravital microscopy [9].

The kinin and the complement systems in the onset of angioedema

The data showing that the vascular leakage induced by SC5b-9 is mediated through the release of BK clearly indicate that the complement and the kinin systems are very closely linked in the stimulation of the endothelium [9]. However it has been shown that other molecules belonging to the complement system are involved in the regulation and activation of the kinin system, such as gC1qR/p33 [15] and C1 inhibitor (C1-INH) [1].

gC1qR/p33, which was originally identified as a receptor for the globular heads of C1q [16], is a binding site for the light chain of high molecular weight kininogen (HK) (Figure 2) and in particular the C-terminal half corresponding to residues 204-218 [17, 18]. Besides gC1qR/p33, HK interacts on the EC surface with the urokinase plasminogen activator receptor (u-PAR) [19] and the cytokeratin-1 (CK-1) [20]. Interestingly, the CK-1 expressed on ECs can be up-regulated under oxidative stress condition and is able to bind MBL, leading to the activation of the lectin complement pathway [21].

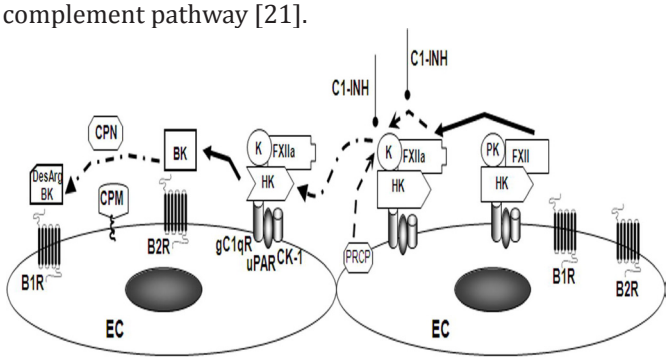

Figure 2. Mechanisms of activation of kinin system along the endothelial cell suface. The trimolecular complex formed by Factor XII, prekallikrein and high molecular kininogen (FXII-PK-HK) interacts with the endothelial cell membrane through a binding site formed by gC1qR/p33, urokinase receptor (uPAR) and cytokeratin 1 (CK-1). The consequent activation of kallikrein (K) by FXIIa and prolylcarboxypeptidase (PRCP) leads to the generation of BK that can stimulate the B2R or can be cleaved by carboxypeptidase M (CPM), on the cell membrane, or CPN, in soluble phase, forming Des-Arg-BK. This is the agonist for B1R which membrane expression is induced by proinflammatory molecules.

gC1qR/p33, uPAR and CK-1 present on the EC surface are able to bind the trimolecular complex formed by prekallikrein (PK), HK and FXII [15, 22]. After this interaction a serine protease (prolylcarboxypeptidase/PRCP), expressed on the cell membrane cleaves PK [23]. The activated kallikrein modifies factor XII leading to its activation that in turn can increase the kallikrein formation on ECs. The main substrate of kallikrein is HK that release the vasoactive peptide BK [15]. All these data suggest that the that gC1qR/p33 may represent a natural surface that modulates or triggers the coagulation/kinin cascade, causing the generation of the potent proinflammatory peptides BK and related kinins (Lys-BK, des-Arg9-BK, Lys-des-Arg9-BK).

It has also been shown that beta-factor XIIa, plasmin and kallikrein are responsible for the activation of the classical and the alternative complement pathways interacting with C1s, C1r and factor B respectively [24], indicating that also molecules of the kinin system can activate the complement cascade.

C1-INH belongs to a family of serine protease inhibitors called serpins that together constitute 20% of all

plasma proteins [25]. It is a glycoprotein of 478 amino acid residues, it is encoded by a single copy gene on chromosome 11 and it is produced by the liver, fibroblasts, monocytes, macrophages, ECs and other cell types [26]. C1-INH is the sole known inhibitor of the C1r and C1s proteases of the first complement component (C1), it inactivates the complex formed by MBL and MASPs [10], inhibits alternative pathway [11], but it is also able to act on the regulation of serine proteases of the clotting system and the kinin system (Factors XIIa and XIa, kallikrein, plasmin, and tissue plasminogen activator), which are activated by injury to blood vessels and by some bacterial toxins [26].

C1-INH deficiency leads to the onset of AE. Although the pathogenesis of the swelling associated with AE was originally thought to be mediated by complement and more specifically by C2-derived kinin, ample evidence now exists that the swelling involves primarily the kinin-forming pathway [2]. Nevertheless, the possibility that activation of both the complement and the kinin-forming systems may contribute to the edema has not been completely excluded. Activated plasma kallikrein, with the contribution of factor XII, initiates the kinin cascade (Figure 2), cleaving HK to generate BK. Nussberger et al. documented that levels of BK was increased in the plasma of patients with AE [27]. FXIIa is also capable of activating C1 and plasmin, leading to the cleavage of C2 into a kinin-like fragment (C2 kinin) [28]. BK, and possibly this fragment, can cause enhanced post-capillary venules permeability presumably mediated by B1R and B2R localized on the endothelial cell membrane [29]. This is responsible for the edema and movement of fluid from the vascular space into the tissues.

The involvement of B2R in the onset of Hereditary AE symptoms is supported by the ameliorative effective obtained treating the patients with HOE-140 (icatibant), a selective antagonist of B2R [30]. Although the time interval observed before onset of symptom relief after the drug administration raise the hypothesis that the maintenance of angioedema may be mediated by other molecules and receptors. The most valid candidates are B1R and gC1qR/p33 which contribution in the release of kinins remains unclear. More recently we used both in vitro and in vivo permeability assays to analyse the ability of the attack phase plasma (APL) from C1-inhbitor deficient patients to caused endothelial leakage [31]. On human adult dermal microvascular ECs and on ECs isolated from the human umbilical vein (HUVECs) APL induced a delayed FITC-BSA leakage (30 minutes) opposed to the rapid effect of BK (5 minutes) while remission plasma (RPL) elicited a modest effect as compared to the control plasma. These data were also confirmed by in vivo experiments. APL, RPL and BK were administered via topical application on rat mesenteric microvessels. APL induced a significant increase in vascular leakage, while RPL had no effect. In the in vitro model the incubation of cultured endothelial cells with a monoclonal antibody against the gC1qR/p33 completely abrogated the permeabilizing effect of APL. HOE-140 induced a partial reduction of APL-induced BSA leakage, as did both B1R antagonists (R715 and R954) and the combined treatment with B1R and B2R antagonists completely inhibited the leakage. Since B2R are constitutively expressed while B1R expression is induced by proinflammatory stimuli such as IL-1β the ECs are treated with this cytokine and then APL from Hereditary AE and Acquired AE patients were added. That treatment induced a further increase of vascular leakage. To further evaluate the role of B1R, brefeldin-A, which is a protein trafficking inhibitor, was used, and that treatment was able to reduce the permeabilizing effect of the APL.

These data suggest that, the interaction between the HK-prekallikren-FXII trimolecular complex and gC1qR/p33 which leads to the formation of BK and des-Arg9-BK, and the expression of B1R represent critical steps in the development of angioedema and the blockade of both B1R and B2R receptors, or of gC1q/p33, may provide novel therapeutic tools to control better the symptoms of the acute attack in patients with angioedema.

Conclusion

On the basis of many experimental evidences reported in this review it is evident that pathological conditions characterized by increase of vascular permeability both the kinin and the complement system are involved. These two systems closely cooperate and the interplay between the complement and the kinin systems is established at different levels: the vascular leakage induced by SC5b-9 is mediated by PAF and BK; the essential role played by C1-INH in controlling both the activation of the complement cascade and many of the serine proteases involved in the clotting and kinin formation processes; the presence of gC1qR/p33 onto the EC surface, where it functions as a receptor for the trimolecular complex HK-PK-FXII leading to the release of BK. All these events clearly indicate that there is a crosstalk between the complement and the kinin systems, and all the activation products coming from both these pathways have a common target, the endothelium. During the angioneurotic edema attacks the deficiency of C1-INH give rise to the activation of the serine proteases, and this activation increases the release of BK through the interaction between HK-PK-FXII and gC1qR/p33. On the EC membrane there are enzymes that can metabolize BK producing the agonist of the B1R which can be upregulated by proinflammatory stimuli such as IL-1β. And this data suggest that the blockade of both B1R and B2R, or of gC1q/p33, may provide novel therapeutic targets to induce symptom relief.

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