Allergology International xxx (2017) 1–4

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Review article

Chronic spontaneous urticaria and the extrinsic coagulation system

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ARTICLE INFO

Article history:
Received 22 August 2017
Accepted 8 September 2017
Available online xxx

Keywords:
Chronic spontaneous urticaria (CSU)
Endothelial cells
Extrinsic coagulation pathway eosinophils
Histamine
Tissue factor (TF)

Abbreviations:
CSU, chronic spontaneous urticarial; TF, tissue factor; PAR, protease activated receptor; HUVEC, human umbilical vein endothelial cells; HMVEC, human dermal microvascular endothelial cells; TLR, Toll-like receptor; LPS, lipopolysaccharide

ABSTRACT

Chronic spontaneous urticaria (CSU) is a common skin disorder characterized by daily or almost daily recurring skin edema and flare with itch. Recently, the activation of the blood coagulation cascade has been suggested to be involved in CSU, but the trigger of the coagulation cascade remains unclear. In this article, we review recent understanding of the relationship between the pathogenesis of CSU and extrinsic coagulation reactions. In CSU, vascular endothelial cells and eosinophils may play a role as TF-expressing cells for activating the extrinsic coagulation pathway. Moreover, the expression of TF on endothelial cells is synergistically enhanced by the activation of Toll-like receptors and histamine H_1 receptors. The activated coagulation factors may induce plasma extravasation followed by degranulation of skin mast cells and edema formation recognized as wheal in CSU. Molecules involved in this cascade could be a target for new and more effective treatments of urticaria.

Pathophysiology of CSU

Chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria (CIU), is a common skin disorder characterized by spontaneously appearing wheals with itch and pruritus anywhere on the body for 6 weeks or longer.[1–4] The crucial role of histamine in CSU has been proven by local release of histamine, which appears to be released from tissue resident mast cells, into the tissue and/or vasculature, and by the clinical efficiency of histamine H_1-receptor antagonists (antihistamines) in patients with urticaria.[5,6] However, the mechanism of mast cell activation in CSU remains largely unclear. The presence of histamine releasing autoantibodies against IgE or the high affinity receptor (FcεRI) on mast cells and basophils may be detected in 30–50% of patients with CSU.[7,8] The involvement of autoantigens has been suggested in view of the rapid effect of omalizumab, an anti-FcεRI monoclonal antibody. However, the continuous presence of autoantibodies and/or autoantigens cannot explain diurnal and local occurrence of wheals observed in CSU. On the other hand, it has been suggested that infections by microorganisms, such as bacteria and/or virus, may be complicated as an underlying cause in many cases of CSU.

Relationship between CSU and the coagulation pathway

The involvement of the coagulation cascade, especially by the extrinsic coagulation pathway, being triggered by the exposure of plasma to tissue factor (TF), also known as factor III, has been demonstrated in the pathogenesis of CSU by a number of observations.[9–14] Several reports suggest that heparin, an anticoagulant which inhibits the activity of coagulation factors, can be effective in the treatment of CSU.[15,16] Moreover, oral anticoagulant drugs, such as warfarin which blocks that activities of factors FVIIa, FXa, and FIIa, may improve clinical symptoms in a certain population of patients with CSU unresponsive to antihistamines.[17] These reports imply that the extrinsic coagulation pathway is directly related to the pathogenesis of CSU. Recently, several groups have shown the increase of blood coagulation markers in patients with CSU.[9–14] Asero and his group showed that in patients with CSU, plasma levels of prothrombin fragment 1 + 2 (PF_{1+2}), a polypeptide of about 34 kD, and D-dimer are higher than those in normal controls

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Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2017.09.003

and correlate with disease severities.[9–11] PF_{1+2} is generated from prothrombin together with thrombin. Once thrombin is produced, it acts on fibrinogen and generates fibrin, which is subsequently stabilized by factor FXIIa and finally degraded by the plasmin pathway (fibrinolysis). D-dimer is produced by the degradation of stabilized fibrin, whereas FDP is produced by fibrinolysis of either stabilized or non-stabilized fibrin. We previously showed the increase of both FDP and D-dimer in patients with CSU, but not in healthy individuals or in patients with inducible type of urticarial (IU), in correlation with disease severity.[18] Moreover, Takeda *et al.* revealed the elevation of blood coagulation potential involving the intrinsic coagulation factors, which enhance the common pathway of coagulation consisting of FVII, FX, FII and fibrinogen.[12,13]

Activation of extrinsic coagulation pathway by TF expressed on cells

Damage to blood vessel walls exposes TF-expressing cells from underlying cell layers to the bloodstream, initiating the extrinsic coagulation cascade with calcium ions.[19,20] High TF expression is found in highly vascularized organs (cells) such as brain (e.g., astrocytes), placenta (e.g., trophoblasts), and lung (e.g., alveolar cells) followed by heart (e.g., cardiac myocytes, pericytes, fibroblasts), kidney, intestine, testes, and uterus (e.g., epithelial cells surrounding the organs). TF is comprised of three domains: an extracellular domain (aa 1-219), followed by a hydrophobic spanning domain (aa 220-242) and a cytoplasmic tail (aa 243-263).[21] The extracellular region contains FVII/VIIa binding domains. The TF-triggered activation of the extrinsic coagulation pathway results in the generation of active serine proteases (coagulant mediators): FVIIa, FXa and thrombin (FIIa). FIIa finally converts fibrinogen to fibrin, leading to fibrin deposition and the activation of platelets to form blood clots. These factors then mediate diverse intracellular activation and production of pro-inflammatory mediators including cytokines, adhesion molecules, and growth factors through protease activated receptors (PAR-1/2/3/4) present on the surface of several cell types.[21,22] FVIIa activates target cells via PAR-2. FXa and FIIa activate various types of cells via PAR-1, 2, 3 and PAR-1, 3, 4, respectively. Fibrin is also able to promote an inflammatory response via Toll-like receptor (TLR)-4 (Fig. 1). Emerging evidence has revealed the

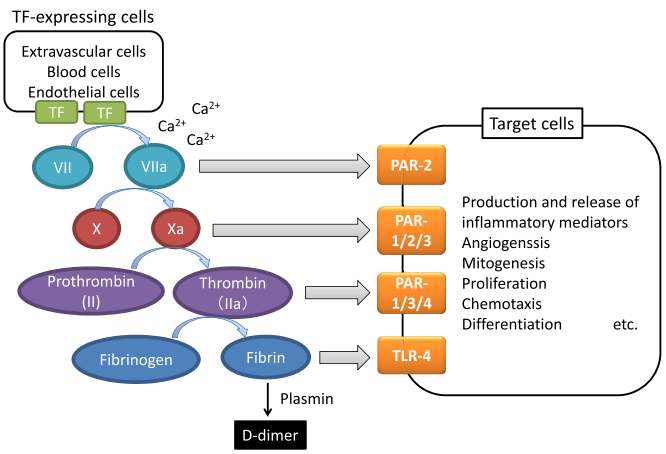

Fig. 1. TF-dependent coagulation pathway and target receptors of the active coagulation factors. Tissue Factor (TF) is able to bind in the presence of calcium to Factor VII (FVII). TF/FVII is activated by auto-cleavage to TF/FVIIa. TF/FVIIa then converts FX to FXa. FXa converts FII (prothrombin) to FIIa (thrombin), which converts fibrinogen to fibrin. D-dimer is produced from fibrin by plasmin. PARs are G-protein-coupled receptors (GPCRs), where PAR-1, 3, 4 transmits FIIa signaling, PAR-1, 2, 3 transmits FXa signaling, and PAR-2 transmits FVIIa signaling. Fibrin is also able to promote an inflammatory response via TLR-4.

involvement of TF in wound repair, embryonic development, angiogenesis, tumor metastasis, cell adhesion/migration, innate immunity and many pathological conditions.

TF expression on eosinophils

In physiological conditions, TF is abundantly expressed in extravascular tissues, but is scarce on the cells exposed to blood circulation. Monocyte, granulocytes, and vascular endothelial cells may express TF on their cell surfaces in contact with the bloodstream, when exposed to bacteria, viruses, and cytokines, such as TNFα, IL-2 and IL-1β in the blood. Recently, Moosbauer *et al.* found activated eosinophils as a major intravascular storage of TF.[23] Their *in vitro* experiments revealed that the expression of TF by eosinophils was enhanced by several cytokines, such as PAF and GM-CSF.[23] Moreover, Asero *et al.* showed a massive expression of TF by eosinophils in the lesional skin tissue of patients with CSU.[24] Furthermore, eosinophils are activated by autoantibodies against the low-affinity IgE receptor (FcεRII), which are detected in about 70% of CSU patients.[25] These reports support the involvement of TF-expressing eosinophils in the skin with the pathogenesis of CSU.

TF expression on vascular endothelial cells

To date, several reports have shown that histamine and LPS, an endotoxin found in the outer membrane of Gram-negative bacteria such as *Helicobacter pylori* and *Yersinia*, independently induced TF expression on vascular endothelial cells, suggesting that TF expressed on endothelial cells may activate the extrinsic coagulation pathway in blood vessels.[26] Nevertheless, the concentration of histamine (1110 ng/ml, equal to 10 μM) required for significant expression of TF on endothelial cells, is much higher than that observed in sera of patients with CSU (<10 ng/ml),[27] and is even higher than that detected in patients with anaphylactic reactions (<100 ng/ml). Moreover, systemic symptoms such as high fever and large increases of C-reactive protein, known as LPS-induced symptoms, are not observed in most patients with CSU.[28] Thus, neither histamine nor LPS seem sufficient to induce the expression of TF triggering the coagulation pathway in patients with CSU. We recently reported that histamine, released from basophils, and LPS synergistically express TF on the surface of vascular endothelial cells, such human umbilical vein endothelial cells (HUVECs) and human dermal microvascular endothelial cells (HMVECs).[29] Moreover, synergistically expressed TF could activate the extrinsic coagulation pathway. Furthermore, active coagulation factors, FXa and IIa, produced by the extrinsic coagulation pathway induced intracellular gap formation between endothelial cells via PAR-1. Fujii *et al.* reported that the activation of the coagulation/fibrinolysis cascade occurs extravascularly as demonstrated by abundant fibrinogen deposits in the dermis of biopsy specimens from urticaria.[30] Our results also imply that the production of activated coagulation factors, such as Xa and IIa, causes intercellular gaps between endothelial cells via PAR-1 and that leakage of plasma into extravascular tissues plays a more important role for edema formation in CSU rather than thrombosis in the vasculature. To explore a mechanism of making endothelial cells more sensitive to histamine, we pre-treated HUVECs with LPS, and revealed an increase of mRNA of H_1 receptors and the enhancement of TF expression in response to histamine. The results suggest that lengthy exposure of endothelial cells to LPS makes HUVECs more sensitive to histamine. Although, we could not detect histamine-induced increase of TLR-4 expression in HUVECs in our experimental conditions, Talreja *et al.* demonstrated that histamine induced TLR-2 and TLR-4 expression in HUVECs and enhanced the sensitivity of HUVECs to LPS.[31] These results imply that histamine and LPS mutually enhance the

Please cite this article in press as: Yanase Y, et al., Chronic spontaneous urticaria and the extrinsic coagulation system, Allergology International (2017), https://doi.org/10.1016/j.alit.2017.09.003