Does Complement Activation Control 'Tissue Trafficking' by C3a and C5a Anaphylotoxin Generation?

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Key Words

Complement
C3a
C5a
Anaphylotoxins
Endothelium
Adherence

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Introduction

Anaphylotoxins C5a and C3a can recruit inflammatory leukocytes to a site of immune complex (IC) lung injury [1–3]. Both C5a and to a lesser extent C3a are chemotactic for inflammatory leukocytes. In vitro studies show that C5a can both up-regulate CD11b/CD18 (B2 integrin) on neutrophils and increase P-selectin on human endothelial cells. Both C3a and C5a induce neutrophil (PMN) aggregation, lysosomal enzyme release from neutrophils and induce bronchial constriction. Thus complement activation can enhance neutrophil binding by PMN B2 integrin up-regulation [4] and adherence to endothelium ICAM-1, and P-selectin up-regulation on endothelium and adherence of PMN L-selectin. Complement depletion with cobra venom factor blocks IC lung injury, possibly by substrate depletion of C3 and C5 and the resultant inability to generate C3a/C5a. Further studies may define analogs capable of interfering with complement-regulated endothelial adherence, which should be useful in blocking complement related inflammation.

Results

Since C3a peptides (C3a57_77) and a synthetic analog peptide (C3a5) have been shown to be as active or more active than native C3a in biologic systems [3] we studied the effect of C3a peptides on human PMN binding to human umbilical vein endothelial cells (HUVECs). Recombinant C5a was also studied. C5a increased binding of PMNs to HUVECs 6-fold. C3a peptides, (1–100 μ M) in contrast did not increase PMN binding. In addition, C5a up-regulated P-selectin on HUVECs and had no effect on ICAM-1 or E-selectin. C3a peptides had no effect on P-selectin, E-selectin, or ICAM-1.

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CD11b/CD18 up-regulation by C5a and C3a peptides In conclusion, C5a up-regulates HUVEC P-selectin as

was also assessed. C5a increased CD11b and CD18 expression on human PMNs by 34 and 45% respectively. C3a peptides did not up-regulate CD11b or CD18 as assessed by flow cytometry. well as CD11b/CD18 receptors. C3a neither up-regulates PMN CD11b/CD18 or HUVEC adhesion molecules. Complement activation results in PMN adherence to endothelial cells, an initial critical step in vasculitis.

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