ANCA reactive B cells and neutrophils cross-talk in the pathogenesis of AAV: A model proposal

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Introduction.– The current model of AAV pathogenesis is based on the role of circulating ANCA and its effect on primed neutrophils. However, published data of patients with AAV treated with Rituximab, which remove circulating B cells, shows that clinical remission correlates more to the decreasing number of circulating B cells than decrease in ANCA titre. Given that ANCA reactive B cells can be found in circulation in patients with AAV, we would like to hypothesize that these cells play a direct role in AAV pathogenesis. Here, we propose a model whereby activated neutrophils and ANCA-reactive B cells engage in intercellular cross-talk, which could potentially lead not only to neutrophil degeneration and inflammation but also to the proliferation and differentiation of ANCA-reactive B cells. The model is based on the expression of complementary molecules on activated B cells and Neutrophils, such as Lymphotoxins (L1a) and ICAM-1 (CD54) on B cells, and LTBR, LAF-1 and BAFF (CD268) molecules on neutrophils. Membrane expression of ANCA antigens on activated neutrophils or in neutrophil-antibody complexes would act as an additional activation signal for B cell differentiation and ANCA production.

Methods.– PBMC from healthy individuals, as well as purified Neutrophils and B cells were cultures in the presence of TLR ligands for 24 and 48 hours. Phenotype studies of B cells and Neutrophils were carried out using directly labelled monoclonal antibodies and analyzed by flow cytometry while the gene expression was studied by RT-PCR.

Results.– Preliminary results show expression of L1a and CD54 on B cells and LTBR and LAF-1 on Neutrophils are modulated by TLR-ligands such as LPS, viral RNA and CpG oligonucleotides. Given the role of these molecules on cell adhesion and activation it is reasonable to speculate on the possibility of neutrophil-B cell and the resulting cell activation. If proven to be true, the model would potentially open new opportunities for disease monitoring and novel targets for therapeutic intervention of AAV.

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Coagulation activity in renal ANCA-positive vasculitis

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Introduction.– Incidence of thromboembolism in ANCA-associated vasculitis (AAV) is high (1–3). The profile of coagulation and fibrinolysis in AAV patients remains poorly characterized and we aimed to study it in association with disease activity in a prospective case control setting.

Methods.– Twenty-one AAV patients with renal disease (median eGFR 21 ml/min) were compared with controls: 20 patients having other mild chronic kidney disease (CKD) (group 2, eGFR 91) and 20 patients with moderate CKD (group 3, eGFR 44). Platelet count, antithrombin (AT), FVIII:C and von Willebrand factor ristocetin cofactor activities (VWF:RCo), VWF antigen (VWF:Ag), fibrinogen, prothrombin fragments (F1 + 2) and fibrin degradation product D-dimer were measured during the active and remission states of the disease and reported as median.

Results.– The F1 + 2 was 2.6-fold and D-dimer 5-fold higher during the active AAV than in its remission (563 vs 212 μM and 3.0 vs 0.6 mg/L, P < 0.01 for both). During active AAV these values clearly exceeded also those of the control group 2 (F1 + 2 164 μM, P < 0.001; D-dimer 0.2 mg/L, P < 0.013) and group 3 (F1 + 2 224 μM; D-dimer 0.3 μM, P < 0.01 for both). Platelet counts and fibrinogen increased during active AAV compared with the remission (294 vs 219 109/L, P < 0.011 and 6.4 vs 4.9 g/l, P = 0.022). Again, FVIII:C (228%), VWF:RCo (198%) and VWF:Ag (222%) were the highest among patients with active AAV, but remained elevated at remission. Interestingly, AT reached supranormal levels towards remission in AAV (101 vs 115%, P < 0.01). In AAV patients, two thromboembolic events occurred during the follow-up.

Conclusion.– Thrombin formation and especially fibrin turnover prevail during active AAV compared both with remission and other kidney