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Complement-cytokine nexus in rheumatoid arthritis

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Abstract

Introduction: Exaggerated complement activation in rheumatoid arthritis may in part be due to the failure of regulatory mechanisms. Complement receptor 1 (CR1) and protectin (CD59) are two important complement regulatory proteins (CRPs) expressed on blood cells. In addition to complement regulation, leukocyte CR1 and CD59 are attributed with immune cell signaling and modulation of adaptive immune responses. Since cytokines are major players in etiology and pathogenesis of systemic auto-immune disorders, it has been our interest to elucidate the correlations of CRPs with cytokines in rheumatoid arthritis. With this aim we studied the expression of leukocyte CR1, CD59 and cytokines (TNF-α, IL-17, IL-18, IFN-γ, IL-10, IL-6 and TGF-β) in 25 healthy individuals (controls) and 35 rheumatoid arthritis patients, evaluated their interrelations and correlations with disease activity parameters (circulating immune complex (CIC), C3, C4 and DAS28 scores), with their voluntary consent and ethical clearance from AIIMS. Methods: Venous blood from the study subjects was collected. PBMCs and neutrophils were isolated by density gradient centrifugation. The expression of CR1, CD59 and cytokines was determined in PBMCs and neutrophils by real-time RT-PCR. Levels of Circulating immune complexes (CIC) in plasma and that of C3 and C4 in serum were determined by PEG precipitation and nephlometry respectively. Results: In patients, expression of CR1 and CD59 in PBMC was significantly reduced and in neutrophils only CR1 expression was reduced as compared to controls. PBMC-CR1 and PBMC-CD59 expression correlated negatively with DAS28 and CIC in patients. In addition, PBMC-CD59 expression correlated negatively with C4 levels in patients. Expression of TNF-α, IL-17, IL-18, IL-10, IL-6 and TGF-β significantly increased whereas that of IFN-γ decreased significantly in PBMC of patients as compared to controls. Expression of TNF-α increased and that of IFN-γ decreased significantly in neutrophils of patients as compared to controls. Expression of TNF-α and IL-18 correlated negatively with CR1 and CD59 expression in PBMCs and positively with CIC and DAS28. IL-10 expression correlated positively with CR1 and CD59 expression in PBMCs and

negatively with CIC and DAS28. Conclusion: We found significant modulation of CR1, CD59 and cytokine expression in rheumatoid arthritis. The correlation of CR1, CD59 with cytokines and disease activity parameters suggest a complex interplay of CRPs with cytokines in relation to disease activity of rheumatoid arthritis.