Ruprecht-Karls-Universität Heidelberg

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Dissertations-Kurzfassung

Predictive value of serological parameters for disease activity in ANCA-associated systemic vasculitis (AASV)

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The association of autoantibodies against myeloid lysozomal antigens or ANCA in Wegener's Granulomatosis (WG), Microscopic Polyangiitis (MPA) and pauci-immune glomerulonephritis is clinically well established. However, the clinical association between the presence and titers of ANCA and disease activity is not clear and remains controversial. Patients with high ANCA titers may stay in remission, whereas relapses in the absence of ANCA have been described. This might be due to the lack of a sensitive and specific diagnostic tool for ANCA detection. In the first chapter, a new generation of ELISA was used by direct coating of recombinant and native proteins. The sensitivity and specificity of conventional direct ELISA, capture ELISA, and this ELISA were compared and related to clinical parameters.

Our data suggest that the employment of the novel Anti-PR-3 ELISA is a useful tool in the diagnostics of WG and especially for the discrimination between patients with active and inactive disease. Apart from ANCA, it is believed that neutrophils play an important role in the pathogenesis of vasculitis. Since FcγRs seem to be essential for activation of neutrophils by ANCA, gene polymorphisms for these receptors have received much attention as genetic factors that might predispose for disease exacerbation. Interestingly, data from Aitman *et.al*, suggest the role of *FcγRIIIb* copy number polymorphism in the genetics of systemic lupus erythematosus (SLE) in rats and humans. However, an association between *FcγRIIIb* copy number variation (CNV) and Anti neutrophil cytoplasmic auto antibodies (ANCA)-associated vasculitis has so far not been studied. In the second chapter, *FcγRIIIb* copy number polymorphism in ANCA-associated vasculitis, we looked in our AASV patient's collective whether an FcγRIIIb copy number polymorphism is present, and whether it is associated with neutrophil dysfunction. In this study we couldn't show any association between *FcγRIIIb* copy number polymorphism and neutrophil dysfunction (e.g. oxidative burst, phagocytosis, and chemotaxis) from AAV patients.

Because neutrophils from AASV patients seem to have a different gene expression signature compared to neutrophils from healthy individuals, it is tempting to speculate that the behavior of the former cells might be different than that of healthy controls.

We therefore tested in chapter three the hypothesis that an impaired degranulation response in conjunction with inadequate inhibition of ROS production occurs when neutrophils from AASV patients are exposed to endothelial cells. Our findings demonstrate that endothelial cells are able to inhibit ROS- and modulate cytokine production upon stimulation of neutrophils or monocytes. Although there was no significant difference between AAV patients and HC in this regard, in active patients neutrophil degranulation might be impaired by endothelial cells. Because degranulation facilitates neutrophil migration, impairment of this process could result in local accumulation of neutrophils in the presence of a chemotactic gradient.