PR3-ANCA POSITIVE ASSOCIATED VASCULITIS IS STRONGLY ASSOCIATED WITH A SPECIFIC MOTIF IN THE PEPTIDE-BINDING CLEFT OF HLA-DP MOLECULES

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INTRODUCTION AND AIMS: ANCA-associated vasculitis (AAV) is characterized by antibodies directed against proteinase-3 (PR3) or myeloperoxidase (MPO). The etiology and pathogenesis of AAV remains largely unknown, but there are clinical, histopathological, epidemiological and genetic differences between PR3-AAV and MPO-AAV. In Europeans PR3-AAV has been shown to be associated with HLA-DPB1*0401 and relapse of PR3-AAV seems to be associated with homozygosity for HLA-DPB1*0401 (Hilborst et al, Arthritis Rheumatol 2017). MPO-AAV has been found to be weakly associated with certain HLA-DQ alleles, but not with HLA-DP (Merkel et al, Arthritis Rheumatol 2017). Lyons et al, NEJM 2012). HLA molecules present autoantigens to T cells and certain pockets of the peptide binding groove of the HLA molecule are especially important for the peptides bound (Wieczorek et al, Front Immunol 2017). The sequence of the amino acids shaping the peptide binding groove are therefore of special interest. To evaluate the possible association of HLA alleles to AAV, we performed HLA typing at genomic sequence resolution of HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1 loci in a genetic homogeneous Caucasian population and the association to the disease burden at onset and clinical outcomes (kidney involvement, multi-organ disease and relapse) among patients with either PR3- or MPO-AAV. Furthermore, sequence analysis of the hypervariable regions in exon 2 of HLA-DPBI (Lauterbach et al, Tissue Antigens 2012) was applied to evaluate if specific sequences of HLA-DPBI alleles associated to AAV contributed to the risk of autoimmune disease.

METHODS: 187 AAV patients and 1074 healthy controls were HLA typed at two-field resolution. The association of HLA alleles to PR3- and MPO-AAV was analyzed. To evaluate the contribution of the dominant molecular motifs of HLA-DPBI molecules associated with AAV, association studies for specific amino acid sequences of the hypervariable regions in exon 2 were performed.

RESULTS: All patients with PR3-AAV were carriers of an HLA-DPBI*04 allele and 85% were homozygous. This differed significantly from the distribution in the control group (p<0.0001). Ninety-four percent were carriers of HLA-DPBI*0401, but the association was even stronger when HLA-DPBI*0402 and -DPB1*2301 also were included (OR 12.1, p<2x10^-29). In the hypervariable regions, HLA-DPBI*0401, -DPB1*0402 and -DPB1*2301 share amino acids in positions 8-9, 69, 76 and 84-87, but only positions 69 and 84-87 contributed significantly to disease risk. Other HLA alleles were only weakly associated with increased or reduced risk of developing PR3-AAV. Interestingly, HLA-DRB1*04 (OR 0.40, p=0.003) were associated with reduced risk of kidney involvement in PR3-AAV. In MPO-AAV, we found only weak associations with HLA class I alleles.

CONCLUSIONS: We confirm that HLA-DPBI*0401 is strongly associated with PR3-AAV and show that the association becomes even stronger when HLA-DPBI*0402 and -DPB1*2301 are included. These three HLA molecules have strong and essential similarities in the amino acids shaping the peptide binding groove, and the association most certainly reflects the presentation of the same autoantigen(s).