

Auto-reactive IgE responses to acidic ribosomal P₂ protein in systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a prototype systemic autoimmune disease characterized by a loss of immune tolerance to self-antigens, uncontrolled production of autoantibodies, and multiple clinical manifestations (1). Several immune disorders are involved in the pathogenesis of the disease, with a central role played by B cells ranging from antibody mediated and antibody independent actions to the presentation of autoantigens and the induction of CD4⁺ T helper cells of Th1, Th2, and Th17 subsets, as well as to the inhibition of regulatory T cells and the secretion of pro-inflammatory cytokines (1).

The autoantibodies found in SLE patients are directed against several cellular components, but mostly against nuclear components. The most prominent ones are disease-specific antibodies directed against double stranded DNA (dsDNA) found in a large proportion of

SLE patients. They are specific for this disease and their presence correlates with the severity and activity of the disease. However, autoantibodies have been also found against other nuclear components, such as small nuclear ribonuclear proteins (Sm), nuclear ribonuclear proteins (nRNP), Ro and other cellular components (1), as well as to acidic ribosomal P proteins (2). P₂ proteins have also been described as minor allergens in fungal allergy where clinically relevant IgE antibodies have been found for Alt a 6, Cla h 4 and Asp f 8, the P₂ ribosomal proteins of *Alternaria alternata*, *Cladosporium herbarum* and *Aspergillus fumigatus* recognized by 8–22% of the patients sensitized to the corresponding moulds (3, 4). Interestingly, patients suffering from allergic bronchopulmonary aspergillosis (ABPA) or severe atopic eczema sensitized to Asp f 8 also show IgE antibodies against P₂ proteins of phylogenetically distant species, including human acidic ribosomal P₂ protein (4, 5). These observations are most likely explainable by cross-reactivity based on molecular mimicry deriving from the high sequence homology shared within the ribosomal P₂ protein family (Fig. 1A) (4). Here we investigated a possible role of IgE-mediated reactions to cross-reactive ribosomal P₂ proteins in SLE. We cloned, expressed and purified ribosomal P₂ proteins of *Homo sapiens*, *A. alternaria*, *A. fumigatus*, *C. herbarum*, and *Saccharomyces cerevisiae* and tested sera of SLE patients for the presence of autoantibodies of the IgG and IgE isotype. From a total of 90 SLE sera analyzed by ELISA, 67 (74%) showed specific IgG and 28 (31%) also specific IgE against human P₂ protein, whereas all

IgE positive sera were also positive for IgG. Moreover, inhibition experiments with solid-phase coated human P₂ protein and homologous P₂ proteins in fluid phase demonstrated that they are capable to fully inhibit IgG (Fig. 1B) as well as IgE-binding (Fig. 1C) to the human self antigen, corroborating the specificity of the IgE-binding found in Western blot analysis (Fig. 1D). These results clearly show that i) sera of a subset of SLE patients contain IgE antibodies against the human P₂ self antigen, and ii) the IgG as well as the IgE-specific autoantibodies are fully cross-reactive with other members of the ribosomal P₂ protein family. However, because the SLE patients investigated are not sensitized to environmental allergens, it is unlikely that the IgE auto- and cross-reactivity to P₂ proteins derives from cross-reactivity resulting from molecular mimicry between environmental allergens and self-antigen. It is tempting to speculate that in this case the IgE derives from a genuine autoimmune reaction to human P₂ protein in SLE patients which are prone to switch B cells toward production of autoantibodies against self antigens. However, the clinical relevance of the observed cross-reactive IgE autoantibodies against P₂ proteins in SLE remains to be elucidated, as it is in most cases of IgE autoreactivity observed in allergic diseases (6).

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Some SLE-patients show IgE-mediated autoreactivity to the P₂ self-antigen not explainable by cross-reactivity with allergens.

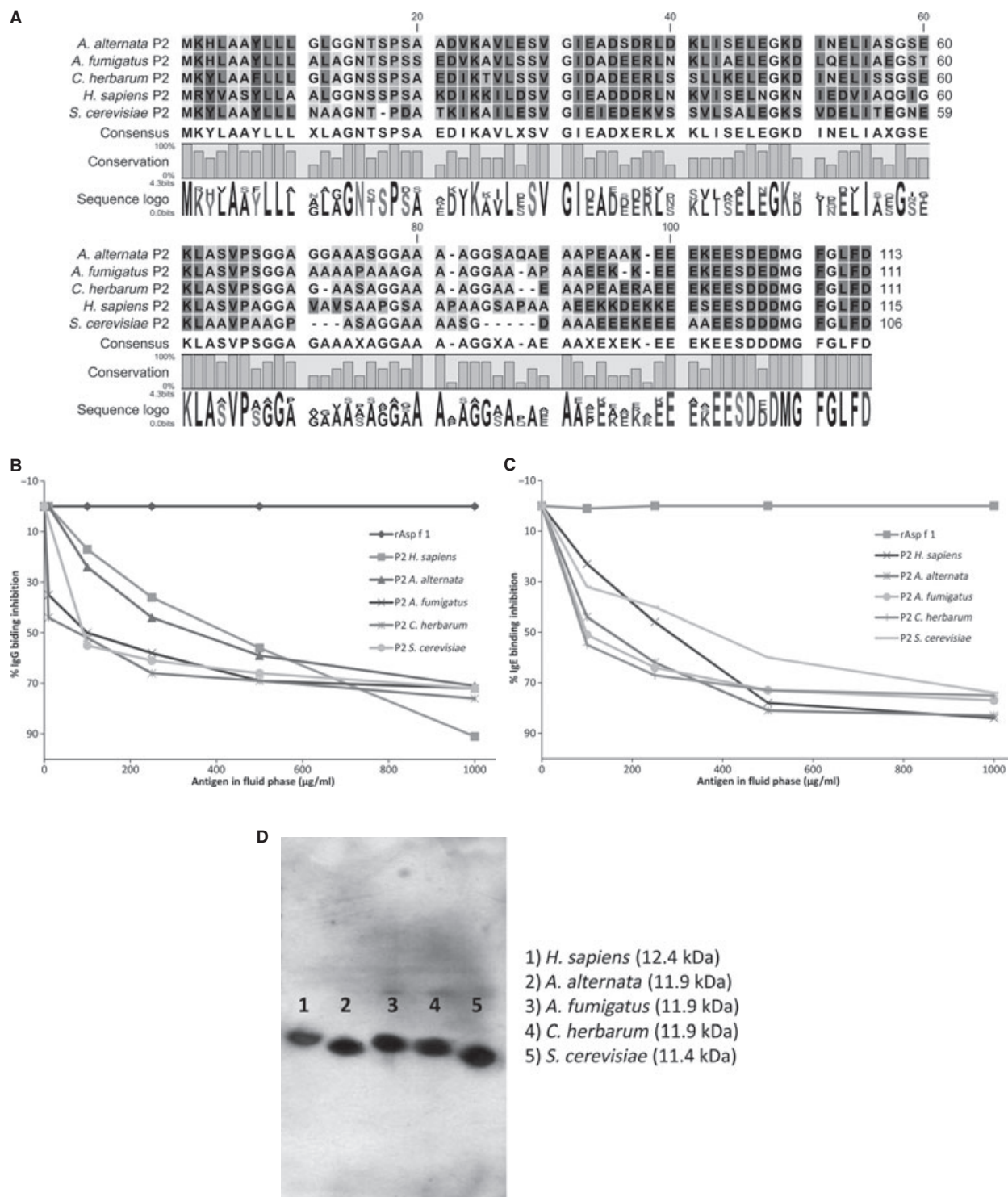


Figure 1 (A) Alignment of the recombinant Proteins: the height of the bar indicates the degree of conservation of an amino acid at a defined position. (B, C) Inhibition ELISA: Antigen was coated on plate (human ribosomal P2 protein) and serum pre-incubated with increasing amounts of soluble antigen was transferred to the plate. ELISA was developed with alkaline phosphatase conjugated anti human IgG (B) or anti human IgE (C) antibody, respectively. (D) Ribosomal P2 proteins were separated with SDS-PAGE, blotted on nitrocellulose membrane and incubated with serum from Systemic lupus erythematosus patients. Binding of specific IgE was detected using anti human IgE mAb TN-142 and developed using labelled secondary antibody.

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