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Auto-reactive IgE responses to acidic ribosomal P_2 protein in systemic lupus erythematosus

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Keywords: autoantibodies; autoreactivity; IgE; ribosomal P2 protein; systemic lupus erythematosus.

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).

Some SLE-patients show IgE-mediated autoreactivity to the P_2 self-antigen not explainable by cross-reactivity with allergens.

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). P_2 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 P_2 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 P_2 proteins of phylogenetically distant species, including human acidic ribosomal P_2 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 P_2 protein family (Fig. 1A) (4). Here we investigated a possible role of IgE-mediated reactions to cross-reactive ribosomal P_2 proteins in SLE. We cloned, expressed and purified ribosomal P_2 proteins of *Homo sapiens*, *A. alternaria*, *A. fumigates*, *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 P_2 protein, whereas all IgE positive sera were also positive for IgG. Moreover, inhibition experiments with solid-phase coated human P_2 protein and homologous P_2 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 P_2 self antigen, and ii) the IgG as well as the IgE-specific autoantibodies are fully cross-reactive with other members of the ribosomal P_2 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 P_2 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 P_2 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 P_2 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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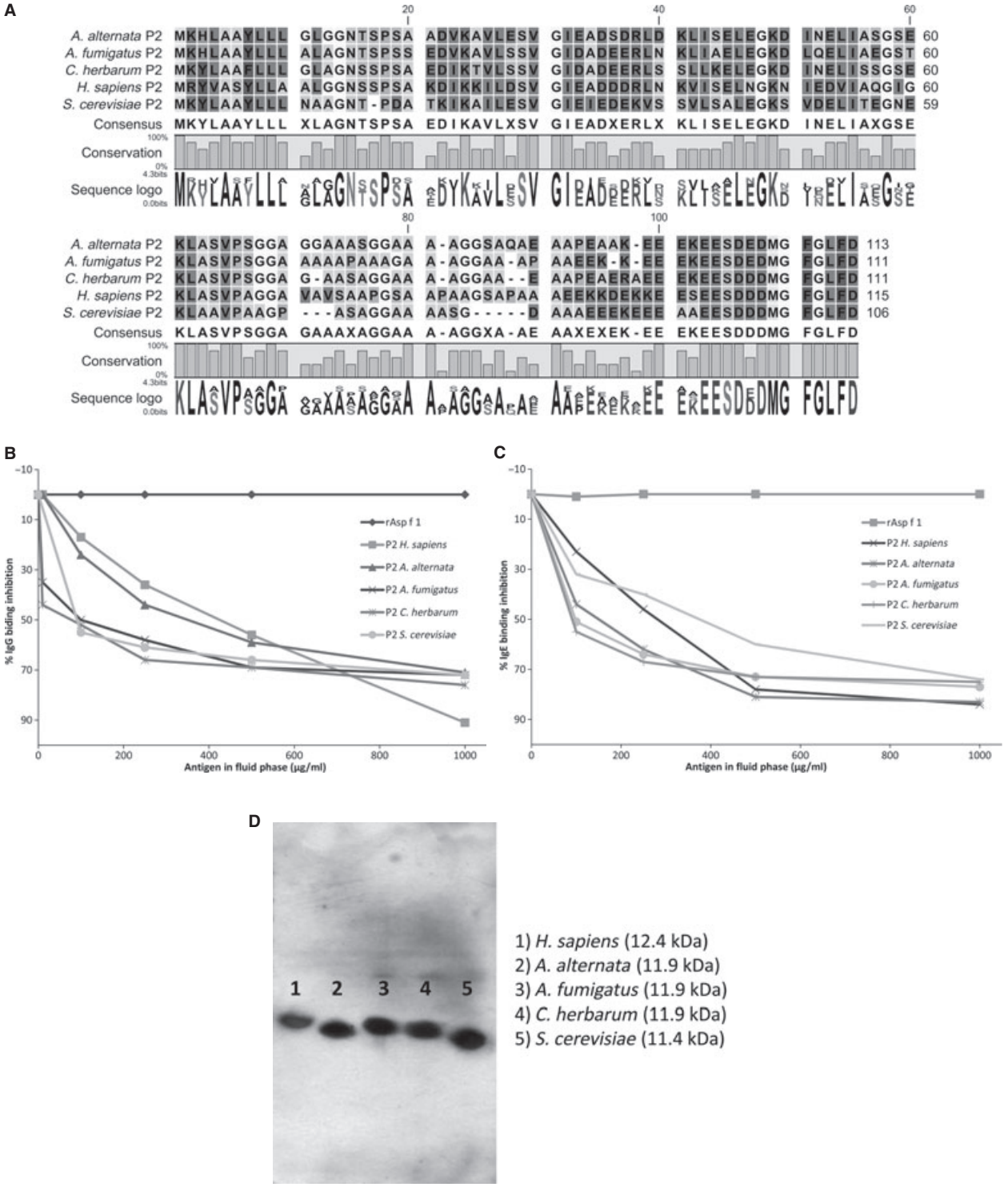

Figure 1 (A) Alignment of the recombinant Proteins: the height of the bar indicates the degree of conservation of an amino acid at a defined position. (B, C) Inhibition ELISA: Antigen was coated on plate (human ribosomal P2 protein) and serum pre-incubated with increasing amounts of soluble antigen was 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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Affected person of a food hypersensitivity – claim of medical achievements in a Luxembourgian medical surgery

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Keywords: costs; food allergy; food hypersensitivity; Luxembourg; medical services.

According to international figures, the prevalence rate of food hypersensitivity varies between 3.24% and 34.9% (1, 2). A review of the literature reveals that no economic data and investigations into food hypersensitivity for the health-care system or the economic losses resulting from this disorder are available (3–5).

This is an analysis of costs to diagnose and treat patients with food hypersensitivity.

Within the scope of the research project MENSSANA (Mobile Expert and Networking System for Systematical Analysis of Nutrition based Allergies), we evaluated the outpatient medical services provided to 46 patients with the clinical picture of food hypersensitivity from October 2008 up to September 2009 (Table 1). The data come from a Luxembourgian medical specialist in dermatology/venereology with further training in allergology. Either food allergy or nonallergic food hypersensitivity had to have been diagnosed or the suspicion of food hypersensitivity in the broader sense had to have been investigated. Furthermore, patients were only included if they were 18 years and older at the time of examination. Overall, 46 patients were identified who fulfilled the designated criteria. Of these 46 people, 33 were women and 13 men. The average age was 43.15 years.

Besides the pure cost survey, the number and distribution of visits to the doctor's office were likewise interesting as a further parameter. The affected persons consulted the practice an average of 2.98 times during this 1-year period (mean 11.42 visits per month). A distortion of the distribution arises here for the month November in which the doctor's practice was closed for 2 weeks (four visits). The 46 patients made most doctor visits exactly in the months of April (19 visits) and July (18 visits) with their high pollen concentrations.

The diagnostic method most often used besides the personal consultation or anamnesis is the radioallergosorbent test. This test was not conducted in only three of the 46 patients; four patients received even two tests. In the process, the blood of the patients was examined

Table 1 Total medical services and expense distribution

(*n* = 46)	Total	Per patient
Practice-related medical services	368	8
Costs	6031.06€	131.11€
Diagnostic methods	188	4.09
Personal consultation/anamnesis	104	2.26
Prick test	22	0.48
Epicutaneous test	15	0.33
RAST	47	1.02
Diamine oxidase	16	0.35
IgE total	40	0.87
Food allergens	287	6.24
Prescribed medications	206	4.48
Costs	5195.92€	112.95€
Absorption of Costs (CNS)	3992.14€	86.79€
Patients' contribution	1203.78€	26.17€
Medical services (incl. laboratory tests) and prescribed drugs	15057.64€	327.34€
Median		323.94€
SD		111.43€
Variance		12416.19€
Minimum		93.17€
Maximum		575.79€
Confidence interval (95%)		[294.25€; 360.43€]