Decreased levels of serum soluble HLA class I antigens in HLA-B27 positive spondyloarthropathies

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uman leucocyte class I antigens (HLA-I) are expressed on the surface of all nucleated cells but can also be found in soluble forms. These soluble HLA-I (sHLA-I) molecules can be produced by either membrane shedding, proteolysis of the intact heavy chain, or by alternative splicing. They have been implicated in regulatory functions and have immunomodulatory properties. Increased levels of sHLA-I were found during graft rejections, in various infectious (cytomegalovirus, hepatitis B or C, HIV infection, active tuberculosis) and autoimmune diseases. In systemic lupus erythematosus and rheumatoid arthritis, levels of sHLA-I antigens correlate with disease activity. Spondyloarthropathies (SpA) are conditions closely linked to HLA-B27, a class I antigen. In this study, we evaluated the serum concentrations of sHLA-I antigens in a large cohort of patients with SpA.

One hundred and twenty three patients who met the European Spondyloarthropathy Study Group criteria for SpA were assessed (table 1). Disease activity was evaluated by the Bath Ankylosing Spondylitis Disease Activity Index and laboratory measures of inflammation (erythrocyte sedimentation rate and serum C reactive protein). The control group comprised 102 healthy subjects (63 male; mean (SD) age 39.5 (3.4)) and included 23 HLA-B27 positive subjects. Determination of sHLA-I antigens was done by a sandwich enzyme linked immunosorbent assay (ELISA; using W6/32 and an anti-β2-microglobulin polyclonal antibody; Bount Laboratories, Milan, Italy).

Patients with SpA had decreased sHLA-I serum levels in comparison with healthy controls (mean (SD) 0.86 (0.6) v 1.18 (0.5) μg/ml; p = 0.0003) (fig 1). HLA-B27 positive SpA showed decreased sHLA-I concentrations in comparison with HLA-B27 negative SpA (0.79 (0.26) v 1.17 (0.7) μg/ml; p = 0.007), while there was no difference between HLA-B27 positive and HLA-B27 negative controls (1.24 (0.5) v 1.17 (0.5) μg/ml; p>0.05). Furthermore, there was no significant difference in sHLA-I concentrations between HLA-B27 negative patients with SpA and HLA-B27 negative controls (1.17 (0.7) v 1.17 (0.5) μg/ml p>0.05), while HLA-B27 positive SpA still had decreased sHLA-I values in comparison with HLA-B27 positive controls (0.79 (0.26) v 1.24 (0.5) μg/ml; p = 0.006). We found no correlation between serum sHLA-I concentration and any of the laboratory and clinical indexes of disease activity (regression analysis, p>0.05).

The significance and role of the sHLA-I antigens still remain unclear. They are present in several body fluids and in synovial fluid from various arthropathies. sHLA-I antigens can bind antigenic peptides and they probably have immunoregulatory functions by the inhibition of cytotoxic T lymphocytes and natural killer cells. Previous studies have suggested that sHLA-I might be used as marker of disease activity or as prognostic factor in autoimmune diseases. On the contrary, in our series of patients with SpA we observed decreased values of sHLA-I. These results were particularly evident in HLA-B27 positive patients with SpA while HLA-B27 did not influence the level of sHLA-I in controls. Thus, both the disease and the HLA-B27 antigen

Table 1 Clinical and biological characteristics of 123 patients with spondyloarthropathies (80 ankylosing spondylitis, 8 reactive arthritis, 10 psoriatic arthritis, 10 enteropathic arthritis and 21 undifferentiated SpA)

| Age (years) | 41 (1.3) |
| Sex (M/F) | 80/43 |
| Disease duration (years) | 8.2 (7.7) |
| ESR (mm/1st h) | 25.0 (26.1) |
| CRP (mg/l) | 23.1 (41.7) |
| HLA-B27 (+) (NDI) | 99/21/3 |
| BASDAI (0–10) | 4.9 (2.0) |
| Extra-articular manifestations, No (%) | 47/123 (38) |
| Peripheral disease, No (%) | 42/123 (34) |

Results are shown as mean (SD), unless indicated otherwise. ESR, erythrocyte sedimentation rate; CRP, C reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; NDI, not determined.
Fibromyalgia

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...between these two groups and according to the presence or absence of HLA-B27.

**P** = 0.005. Horizontal lines represent mean values.

Figure 1 Soluble HLA class I antigens (sHLA-I) were measured by ELISA in the serum from 123 patients with spondyloarthropathies and 102 healthy controls. Results, expressed in ng/ml, were compared (Student’s t test) between these two groups and according to the presence or absence of HLA-B27.

sHLA-I molecules could not be used as markers for the evaluation or for the follow up of these diseases.

Differences in factors have been related to the production of sHLA-I antigens: genetic backgrounds, HLA-I haplotypes, treatments such as non-steroidal anti-inflammatory drugs. HLA-B27 can form heavy chain homodimers. It is not currently known whether these HLA-B27 homodimers might influence the release or production of sHLA-I. However, such a low level of serum sHLA-I in SpA may interfere with immune regulation or cytotoxic T lymphocyte and natural killer cell control, and this might contribute to the pathophysiology of the SpA. Further studies are required to evaluate the soluble forms of HLA-B27.

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