Polymorphisms in the selenoprotein S gene: lack of association with autoimmune inflammatory diseases

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Abstract

Background: Selenoprotein S (SelS) protects the functional integrity of the endoplasmic reticulum against the deleterious effects of metabolic stress. SEPS1/SelS polymorphisms have been involved in the increased release of pro-inflammatory cytokines interleukin (IL)-1β, tumor necrosis factor (TNF)-α and IL-6 in macrophages. We aimed at investigating the role of the SEPS1 variants previously associated with higher plasma levels of these cytokines and of the SEPS1 haplotypes in the susceptibility to develop immune-mediated diseases characterized by an inflammatory component.

Results: Six polymorphisms distributed through the SEPS1 gene (rs11327127, rs28665122, rs4965814, rs12917258, rs4965373 and rs2101171) were genotyped in more than two thousand patients suffering from type 1 diabetes, rheumatoid arthritis or inflammatory bowel diseases and 550 healthy controls included in the case-control study.

Conclusion: Lack of association of SEPS1 polymorphisms or haplotypes precludes a major role of this gene increasing predisposition to these inflammatory diseases.

Background

The human gene SEPS1, located on chromosome 15q26.3, encodes selenoprotein S which participates in the retro-translocation of misfolded proteins from the endoplasmic reticulum (ER) to the cytosol for their degradation [1]. This ER membrane protein functions in stress responses to prevent the deleterious consequences of accumulation of misfolded proteins, accumulation that has been linked to immune and inflammatory processes [2]. A study identified the strong association of the proxi-
nal promoter SEPS1 polymorphism at -105G/A with circulating levels of three pro-inflammatory cytokines, interleukin (IL)-6, IL-1β and TNF-α [3]. Moreover, these authors reported that the mutant variant significantly reduced the promoter activity of the SEPS1 gene in stressed HepG2 cells and that the suppression of this gene by short interfering RNA increased the release of pro-inflammatory cytokines in a macrophage cell line. A regulatory loop has been recently proposed whereby cytokines stimulate the expression of SEPS1, which in turn diminishes cytokine production [4].

The murine homolog gene of the human SEPS1 is the Tanis gene, which encodes a serum amyloid A receptor [5]. Acute phase serum amyloid A proteins (SAAs) are multifunctional apolipoproteins produced in large amounts during the acute phase of inflammation and also during the development of chronic inflammatory diseases. SAAs are involved in the pathogenesis of several chronic inflammatory diseases, such as rheumatoid arthritis (RA) [6-9], multiple sclerosis (MS) [10] and inflammatory bowel diseases (IBD) [11-13]. It is believed that locally synthesized SAA by synovial cells in the inflamed joints acts as an autocrine inducer of matrix metalloproteinase-1 and causes extensive joint erosion [14].

Altogether these data point to the important role of selenoprotein S mediating inflammation, and we aimed at testing whether the SEPS1 gene was involved in the development of inflammatory autoimmune complex diseases. These are multifactorial traits influenced by both genetic predisposing factors and environmental triggers. The activation of SEPS1 expression by fasting in vivo and by glucose-deprivation in vitro allowed its assignation to the glucose-regulated protein family [5,15]. Furthermore, a locus on 15q26, IDDM3, was described to increase susceptibility to type 1 diabetes, T1D [16,17]. Therefore, we decide to test the SEPS1 polymorphisms for association with diabetes risk in a cohort of Spanish T1D patients. Additionally, we pursued to study two other autoimmune diseases with an important inflammatory component, rheumatoid arthritis and the inflammatory bowel diseases, Crohn’s disease (CD) and ulcerative colitis (UC). Provided this candidate gene previously related with the inflammatory response shows any influence on the pathogenesis of these diseases, a new mechanistic tool for treatment would be available.

Methods

Patients and controls

The study group consisted of 592 RA, 674 IBD and 311 T1D unrelated patients, consecutively recruited from one centre, either Hospital Clínico San Carlos or Hospital Ramón y Cajal (Madrid, Spain).

T1D patients (median age at onset 15 years) diagnosed according to the criteria of the American Diabetes Association (ADA), were insulin-dependent at the time to study.

RA diagnosis was established based on the American College of Rheumatology (ACR) criteria [18] and samples were previously genotyped for HLA-DRB1. Mean age at onset was 54 ± 14 years; 61% of the patients carried the shared epitope; 66% and 50% of the patients were positive for rheumatoid factor and for anti-cyclic citrullinated peptide, respectively, and 32% of the patients presented nodular disease.

Diagnosis of IBD patients was based on standard clinical, radiologic, endoscopic and histologic criteria [19]. The mean age at onset for UC patients was 38 years; 41% of the patients presented pancolitis; 47% and 13% of the patients suffered extraintestinal manifestations and colectomy, respectively. CD patients were classified according to the location of the lesions in ileal (L1, 48%), colonic (L2, 16%), ileocolonic (L3, 32%) and upper gastrointestinal tract (L4, 3%) and according to the disease behavior in inflammatory (B1, 43%), strictureing (B2, 15%) and perforating (B3, 42%). Only 20% of the CD patients debuted after the age of 40.

A group of 550 healthy unrelated subjects from Madrid (mainly hospital employees and blood donors) were selected as controls. Cases and controls were all white Spanish subjects and were included in this study after written informed consent. The Ethics Committee of Hospital Clínico (Madrid) approved the study.

SEPS1 polymorphisms

The SEPS1 polymorphisms (rs11327127, rs28665122, rs4965814, rs12917258, rs4965373 and rs2101171) were genotyped using TaqMan assays from Applied Biosystems following manufacturer’s suggestions and analyzed in an ABI 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). Their location is indicated by the distance from the transcription start site: two of them are in the promoter region; another two in intron 5; rs4965373 depending of alternative splicing is either in intron 6 or in the 3’UTR region; and the last one is downstream at 9707 (see Table 1).

Statistical Analysis

Allele and genotype frequencies in patients and controls were compared by χ² test or Fisher exact test when necessary; p values were considered significant at a level of <0.05. Odds ratio (OR) and p values were calculated using a standard package (Epi Info v. 6.02, CDC, Atlanta, USA). For an OR = 1.5, the statistical power of our cohorts ranged from 80 – 95% depending on the specific polymorphism analyzed.
Haplotypic frequencies were estimated using the Expectation-Maximization algorithm implemented in the Arlequin v2.000 software [20] with number of iterations set at 5000 and initial conditions at 50, with an epsilon value of $10^{-7}$.

**Results and discussion**

The present study investigates the influence of all SEPS1 variants previously correlated with increased pro-inflammatory cytokines levels (polymorphisms at -105G/A, 3705G/A and 5227C/T) and of the SEPS1 haplotypes on predisposition to inflammatory complex diseases.

We first analyzed the functional SEPS1 promoter polymorphism at -105G/A and no significant differences in genotypic frequencies were observed when healthy controls were compared with patients suffering from T1D, RA or IBD (Table 1). As two other variants (rs4965814 and rs4965373) have been associated with high plasma cytokine levels [3], we studied them in our cohorts, and the distribution of genotypes followed the same pattern in patients and in controls (Table 1).

We selected three additional polymorphisms along the gene from those described by Curran et al [3] in order to analyze the haplotypes inferred by applying the Expectation-Maximization algorithm implemented in the Arlequin software. No significant difference in haplotype frequencies was observed after appropriate correction for multiple testing in any diseased cohort (Table 2).

A direct functionality has been attributed to the SEPS1 promoter polymorphism at -105G/A, increasing plasma levels of the aforementioned cytokines presumably due to the disruption of an ER stress element (ERSE). Two other tested variants have also been strongly related with the circulating levels of the inflammatory cytokines [3]. In contrast, a recent report did not find consistent association of this polymorphism with circulating levels of either IL-6 or TNF-α [21]. We did not observe differences in the genotypic distribution of the SEPS1 polymorphisms analyzed in Spanish cohorts between patients suffering from autoimmune diseases with a clear inflammatory component, like T1D, RA or IBD, and controls. The analysis of SEPS1 haplotypic frequencies did not differ between patients and healthy individuals either.

Given that evidences exist for the affected expression and activity of some selenoproteins depending on sexual dimorphism in mouse [22] and human [23], we decided to check for a gender specific association of -105G/A SEPS1 polymorphism with the autoimmune disorders under study; however, we did not detect a gender-bias in our results. No significant difference between sex-stratified cohorts was found for any of the polymorphisms studied (Table 3).

| Polymorphism | T1D patients | RA patients | CD patients | UC patients | Controls |
|--------------|--------------|-------------|-------------|-------------|----------|
| -538 SEPS1   |              |             |             |             |          |
| **rs11327127** |              |             |             |             |          |
| TT           | 103 (59%)    | 212 (59%)   | 218 (62%)   | 235 (62%)   | 306 (60%) |
| T delT       | 106 (34%)    | 127 (35%)   | 111 (32%)   | 124 (32%)   | 180 (35%) |
| delT delT    | 21 (7%)      | 20 (6%)     | 21 (6%)     | 22 (6%)     | 28 (5%)   |
| -105 SEPS1   |              |             |             |             |          |
| **rs28665122** |              |             |             |             |          |
| CC           | 216 (70%)    | 253 (70%)   | 253 (73%)   | 274 (71%)   | 360 (72%) |
| CT           | 85 (27%)     | 92 (26%)    | 83 (24%)    | 100 (26%)   | 124 (25%) |
| TT           | 9 (3%)       | 14 (4%)     | 12 (3%)     | 11 (3%)     | 14 (3%)   |
| SEPS1 3705  |              |             |             |             |          |
| **rs4965814** |              |             |             |             |          |
| TT           | 195 (63%)    | 224 (62%)   | 215 (68%)   | 225 (64%)   | 334 (65%) |
| TC           | 103 (33%)    | 118 (33%)   | 82 (26%)    | 112 (32%)   | 161 (31%) |
| CC           | 12 (4%)      | 17 (5%)     | 19 (6%)     | 12 (4%)     | 20 (4%)   |
| SEPS1 4283  |              |             |             |             |          |
| **rs12917258** |              |             |             |             |          |
| CC           | 148 (48%)    | 150 (42%)   | 164 (46%)   | 165 (44%)   | 215 (42%) |
| CG           | 137 (44%)    | 163 (45%)   | 149 (42%)   | 173 (46%)   | 247 (48%) |
| GG           | 25 (8%)      | 46 (13%)    | 40 (11%)    | 38 (10%)    | 49 (10%)  |
| SEPS1 5227  |              |             |             |             |          |
| **rs4965373** |              |             |             |             |          |
| GG           | 145 (47%)    | 187 (52%)   | 182 (52%)   | 178 (48%)   | 246 (48%) |
| GA           | 127 (41%)    | 142 (40%)   | 136 (39%)   | 163 (43%)   | 220 (43%) |
| AA           | 38 (12%)     | 30 (8%)     | 33 (9%)     | 33 (9%)     | 43 (9%)   |
| SEPS1 9707  |              |             |             |             |          |
| **rs2101171** |              |             |             |             |          |
| TT           | 177 (57%)    | 218 (61%)   | 216 (61%)   | 223 (59%)   | 296 (58%) |
| TC           | 113 (37%)    | 130 (36%)   | 122 (34%)   | 138 (37%)   | 191 (37%) |
| CC           | 20 (6%)      | 11 (3%)     | 16 (5%)     | 17 (4%)     | 26 (5%)   |
SEPS1 expression was not significantly altered in intestinal epithelial cells of IBD murine models or in intestinal biopsies from IBD patients when compared with that present in controls [24]. Concordantly, a study testing the association of the promoter variant at -105 with cerebrovascular disease found no influence on stroke risk [25]. Both studies are in agreement with our results that showed lack of association between SEPS1 polymorphisms and susceptibility to chronic inflammatory diseases. Moreover, a Finnish study of five variants in the SEPS1 gene locus showed no significant difference between carriers/non-carriers when cardiovascular cases

Table 2: Haplotypes estimated within the SEPS1 gene (alleles at -538/-105/3705/4283/5227/9707) and their distribution in patients and healthy individuals.

|          | T1D (n = 620) | RA (n = 718) | CD (n = 582) | UC (n = 664) | Controls (n = 982) |
|----------|---------------|-------------|--------------|--------------|--------------------|
| Freq.    | HT            | Freq.       | HT           | Freq.        | HT                |
| TCTGGT   | 0.28827       | 179         | 0.32557      | 234          | 0.334699          | 195               | 0.339168          | 225               | 0.325571          | 320               |
| TCTCGT   | 0.1716        | 106         | 0.1711       | 123          | 0.185524         | 108               | 0.176243          | 117               | 0.171104          | 168               |
| TCTCAC   | 0.16575       | 103         | 0.15691      | 113          | 0.140554         | 82                | 0.161364          | 107               | 0.156905          | 154               |
| DelT TCCGT | 0.13375     | 83          | 0.12057      | 87           | 0.124047         | 72                | 0.122667          | 81                | 0.120574          | 118               |
| DelT TCTCAC | 0.06887    | 43          | 0.07503      | 54           | 0.063144         | 37                | 0.051819          | 34                | 0.075028          | 74                |
| TCTCAT   | 0.07046       | 44          | 0.05216      | 37           | 0.069939         | 41                | 0.060517          | 40                | 0.059218          | 51                |
| TCCCCGT  | 0.02949       | 18          | 0.02635      | 20           | 0.027632         | 16                | 0.027826          | 18                | 0.026349          | 26                |
| TCTCCGT  | 0.01231       | 8           | 0.01671      | 12           | 0.011366         | 7                 | 0.010658          | 7                 | 0.018029          | 18                |
| DelT CCCGT | 0.00875    | 5           | 0.01114      | 8            | 0.019499         | 11                | 0.015959          | 11                | 0.015536          | 15                |
| Others   | 0.05075       | 31          | 0.04178      | 30           | 0.023596         | 13                | 0.033779          | 24                | 0.038746          | 38                |

Table 3: Genotype frequencies of SEPS1 polymorphisms in Spanish patients stratified by gender.

|          | T1D Women (n, %) | T1D Men (n, %) | RA Women (n, %) | RA Men (n, %) | CD Women (n, %) | CD Men (n, %) | UC Women (n, %) | UC Men (n, %) |
|----------|------------------|----------------|-----------------|--------------|-----------------|--------------|-----------------|--------------|
| -538 SEPS1 | rs11327127       |                |                 |              |                 |              |                 |              |
| TT       | 90 (58)          | 93 (60)        | 160 (59)        | 49 (60)      | 108 (60)        | 109 (64)     | 97 (64)         | 135 (60)      |
| T delT   | 53 (34)          | 53 (34)        | 100 (37)        | 24 (30)      | 61 (34)         | 50 (30)      | 49 (33)         | 72 (32)       |
| delT delT | 12 (8)          | 9 (6)          | 12 (4)          | 8 (10)       | 10 (6)          | 10 (6)       | 4 (3)           | 18 (8)        |
| -105 SEPS1 | rs28665122     |                |                 |              |                 |              |                 |              |
| CC       | 107 (69)         | 109 (70)       | 191 (70)        | 58 (71)      | 128 (72)        | 123 (73)     | 106 (71)        | 160 (71)      |
| CT       | 43 (28)          | 42 (27)        | 70 (26)         | 20 (25)      | 44 (25)         | 38 (23)      | 42 (28)         | 56 (25)       |
| TT       | 5 (3)            | 4 (3)          | 11 (4)          | 3 (4)        | 5 (3)           | 7 (4)        | 2 (1)           | 9 (4)         |
| SEPS1 3705 | rs4965814      |                |                 |              |                 |              |                 |              |
| TT       | 99 (64)          | 96 (62)        | 172 (63)        | 49 (60)      | 109 (68)        | 104 (68)     | 92 (69)         | 129 (62)      |
| TC       | 50 (32)          | 53 (34)        | 87 (32)         | 28 (35)      | 43 (27)         | 40 (26)      | 38 (29)         | 70 (34)       |
| CC       | 6 (4)            | 6 (4)          | 13 (5)          | 4 (5)        | 8 (5)           | 10 (6)       | 3 (2)           | 9 (4)         |
| SEPS1 4283 | rs12917258     |                |                 |              |                 |              |                 |              |
| CC       | 82 (53)          | 66 (43)        | 109 (40)        | 39 (48)      | 78 (43)         | 84 (50)      | 69 (47)         | 92 (41)       |
| CG       | 61 (39)          | 76 (49)        | 124 (46)        | 35 (43)      | 85 (47)         | 63 (37)      | 59 (40)         | 113 (51)      |
| GG       | 12 (8)           | 13 (8)         | 39 (14)         | 7 (9)        | 17 (9)          | 23 (13)      | 20 (13)         | 18 (8)        |
| SEPS1 5227 | rs4965373      |                |                 |              |                 |              |                 |              |
| GG       | 71 (46)          | 74 (48)        | 150 (55)        | 34 (42)      | 92 (51)         | 89 (53)      | 74 (51)         | 102 (46)      |
| GA       | 61 (39)          | 66 (42)        | 103 (38)        | 37 (45)      | 72 (40)         | 62 (37)      | 51 (35)         | 105 (48)      |
| AA       | 23 (15)          | 15 (10)        | 19 (7)          | 10 (12)      | 16 (9)          | 17 (10)      | 20 (14)         | 13 (6)        |
| SEPS1 9707 | rs21011711     |                |                 |              |                 |              |                 |              |
| TT       | 87 (56)          | 90 (58)        | 172 (63)        | 43 (53)      | 111 (61)        | 105 (61)     | 96 (64)         | 124 (55)      |
| TC       | 65 (36)          | 58 (37)        | 91 (34)         | 36 (44)      | 64 (35)         | 56 (33)      | 40 (27)         | 95 (43)       |
| CC       | 13 (8)           | 7 (5)          | 9 (3)           | 2 (3)        | 6 (3)           | 10 (6)       | 13 (9)          | 4 (2)         |
and healthy individuals were compared. The authors suggested that two polymorphisms contribute to the risk for coronary heart disease and for ischemic stroke in females; interestingly, the associated polymorphisms do not correspond with the one at -105G/A [21]. Therefore, evidences are mounting against the role of the SEPS1 gene in all these conditions, with the only exception to this point of one report defining the minor allele at -105G/A SEPS1 as a risk factor for preeclampsia in a large Norwegian cohort [26].

Conclusion
The Wellcome Trust Case Control Consortium published recently a genome wide association study for several inflammatory conditions, such as RA, T1D or CD [27] although the chromosomal region where the gene maps did not show association for any of the mentioned diseases, the SEPS1 polymorphisms were not analyzed and therefore their involvement in susceptibility could not be formally excluded. Ours is a thorough study analyzing the influence of six polymorphisms along the SEPS1 gene on susceptibility to common diseases, unravelling lack of association. Our data allow discarding a major individual role of this gene in the aetiology of the studied polygenic diseases.

Abbreviations
SelS(SEPS1): Selenoprotein S gene; (IL)-1β: Interleukin 1 beta; TNF-α: Tumor necrosis factor alpha; IL-6: Interleukin 6; ER: Endoplasmic reticulum; HepG2: Human hepatocellular liver carcinoma cell line; RNA: Ribonucleic acid; SAAs: Acute phase serum amyloid A proteins; RA: Rheumatoid arthritis; MS: Multiple sclerosis; IBD: Inflammatory bowel diseases; IDDM3: Insulin-dependent diabetes mellitus 3; T1D: Type 1 diabetes; CD: Crohn's disease; UC: Ulcerative colitis; ERSE: ER stress element; ADA: American Diabetes Association; ACR: American College of Rheumatology; L1: Ileal lesions; L2: Colonic lesions; L3: Ileoceleonic lesions; L4: Upper gastrointestinal tract lesions; B1: Inflammatory disease behavior; B2: Structuring disease behavior; B3: Perforating disease behavior; OR: Odds ratio; FIS: Fondo de Investigaciones Sanitarias.

Authors' contributions
JLS, JV and AnM, carried out the genotyping of the patients and a great part of the controls, participated in the statistical analysis and drafted the manuscript. JLM, HdlC, MDR, JRL and BFG made the diagnosis and collaborated in collection of samples. AM participated in the coordination of the study and participated in the statistical analysis. EGdLC coordinated the study and critically revised the manuscript. EU conceived of the study, participated in the statistical analysis and completed the writing of the manuscript. All authors read and approved the final manuscript.

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