Increased Production of the Soluble Tumor-Associated Antigens CA19-9, CA125, and CA15-3 in Rheumatoid Arthritis

Potential Adhesion Molecules in Synovial Inflammation?

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ABSTRACT: Some tumor-associated antigens (TAAs) are expressed on inflammatory cells. We previously detected carcinoembryonic antigen (CEA; CD66) in the rheumatoid (RA) synovium. The production of CEA, CA19-9, CA125, and CA15.3, may be increased in patients with RA, scleroderma, lupus, and Sjögren's syndrome (SS). Some of these TAAs contain sialylated carbohydrate motifs and they are involved in tumor-associated cell adhesion and metastasis. We assessed levels of

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Ann. N.Y. Acad. Sci. 1408: 359–371 (2007). **© 2007 New York Academy of Sciences.**
doi: 10.1196/annals.1422.037

TAAs in the sera of RA patients and healthy subjects. Serum TAA levels were correlated with disease markers including serum rheumatoid factor (RF), C-reactive protein (CRP), and anti-CCP antibody levels, DAS28, age disease duration. TAAs including CEA, CA15-3, CA72-4, CA125, and CA19-9, and neuron-specific enolase (NSE) were assessed by immunoassay in the sera of 75 patients with RA and 50 age- and sex-matched healthy controls. Normal upper limits for these TAAs were 3.4 μg/L, 25 kU/L, 6.9 kU/L, 35 kU/L, 34 kU/L, and 16.3 μg/L, respectively. There were significantly more RA patients showing abnormally high levels of CA125 (10.8% versus 7.1%), CA19-9 (8.1% versus 0%), and CA15-3 (17.6% versus 14.3%) in comparison to controls ($P < 0.05$). The mean absolute serum levels of CA125 (23.9 ± 1.8 versus 16.8 ± 2.2 kU/L) and CA19-9 (14.2 ± 1.2 versus 10.5 ± 1.6 kU/L) were also significantly higher in RA compared to controls ($P < 0.05$). Among RA patients, serum CEA showed significant correlation with RF ($r = 0.270$; $P < 0.05$). None of the assessed TAAs showed any correlation with CRP, anti-CCP, DAS28, age or disease duration. The concentration of some TAAs may be elevated in the sera of patients with established RA in comparison to healthy subjects. CEA, CA19-9, CA125, and CA15-3 contain carbohydrate motifs and thus they may be involved in synovitis-associated adhesive events. Furthermore, some TAAs, such as CEA, may also correlate with prognostic factors, such as serum RF levels.

KEYWORDS: **rheumatoid arthritis; tumor antigens; anti-CCP antibody; rheumatoid factor; carcinoembryonic antigen**

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that affects approximately 0.5–1% of the population. Chronic synovitis in RA may eventually lead to joint destruction. The etiology of the disease is still unknown, however, both genetic and environmental factors play an important role in the onset of RA. The follow-up of patients including the determination of disease activity and prognostic markers is very important for the introduction of effective therapeutic strategies and for disease outcome.[1]

Several laboratory markers including autoantibodies have been associated with disease activity and/or prognosis of RA.[1] IgM rheumatoid factor (RF) is a good prognostic marker, but does not follow disease activity. It has rather low specificity for RA.[2] C-reactive protein (CRP) is a convenient and sensitive marker of inflammatory activity in clinical practice. The control of inflammation by antirheumatic therapy usually leads to suppression of serum CRP levels.[3] Anticyclic citrullinated peptide (CCP) has been identified as a diagnostic and prognostic marker of RA. The presence of anti-CCP antibodies is highly specific and sensitive for RA. Anti-CCP is a prognostic marker, as it may predict persistent, erosive, more aggressive synovitis.[4,5] Some investigators found a correlation between anti-CCP and RF positivity.[6,7] However, others found no such relationship.[8]

TABLE 1. Tumor-associated antigens

CEA	180 kDa sLe-x: adhesion	Colon, pancreas, lung
CA15-3	300–450 kDa MUC1: adhesion	Breast
CA19-9	sLe-a: adhesion	Colon, pancreas, biliary
CA125	200 kDa MUC16: adhesion	Ovary
CA72-4	400 kDa gp	GI, ovary, lung
NSE	87 kDa enolase	Neuroblastoma, lung

There have been reports showing that tumor-associated antigens (TAAs) may, apart from cancer cells, become expressed on the surface of inflammatory cells. These TAAs may play a role in the perpetuation of inflammation. Some may even serve as cell adhesion receptors. These TAAs may shed from the cell surface and can be readily detected in the sera of cancer patients.[9–12]

Perhaps the most well-known TAAs are the CD66 antigens, or the carcinoembryonic antigen (CEA) family. The five members of this TAA family, CD66a-e, belong to the immunoglobulin superfamily of cell adhesion molecules (CAM).[9,13,14] These antigens contain carbohydrate motifs including Lewis-x (Le-x) and sialyl-Lewis-x (sLe-x) and they are present on colorectal and gastric carcinoma cells.[15,16] However, besides being present on tumor cells, CD66 antigens were described for the first time to be present on inflammatory leukocytes as well.[9,15,17–19] The CD66 molecules mediate the adhesion of tumor cells and neutrophils to activated endothelium during metastasis formation and inflammation, respectively. CD66 antigens bind to E-selectin.[14,15,20] We and others detected CEA-related antigens (CD66b and CD66c) on neutrophils and monocyte/macrophages.[9,15,19,21] In addition, we and others detected an increased expression of CD66 in the RA synovial tissue in comparison to normal synovia.[9,19]

Apart from the CEA family, other TAAs may also be associated with inflammatory diseases. Among these TAAs, CA15-3 is expressed on breast carcinoma, CA19-9 on pancreatic carcinoma, CA125 on ovarian carcinoma, CA72-4 on gastric and mucinous ovarian carcinoma, and neuron-specific enolase (NSE) on small-cell lung carcinoma and neuroblastoma (TABLE 1). Recent scattered studies revealed that some of these TAAs may also be present in patients with other autoimmune diseases.[22–26] Abundant CA19-9 was detected in the sera of some RA,[22] systemic sclerosis (SSc),[23] primary Sjögren's syndrome (SS),[10,26] mixed connective tissue disease (MCTD),[10] and myositis patients.[10] Increased CA125 production has been associated with pleural effusion in SSc and systemic lupus erythematosus (SLE).[23,25] Furthermore, serum CA15-3 levels were elevated in a subset of SSc with severe lung involvement.[24] However, little information is available on the association of TAAs described above and RA.

Not only members of the CD66 family, but also other TAAs may act as CAM. CA19-9, CA125, and CA15-3 contain carbohydrate determinants and they are involved in the adhesive properties of tumor cells and possibly inflammatory leukocytes. Sialyl-Lewis-a (sLe-a), a blood group antigen, is the immune determinant of CA19-9. sLe-x and sLE-a are ligands of E-selectin.[27] CA125 is also known as MUC16, a giant mucin-like glycoprotein, which mediates ovarian cancer cell adhesion.[11] CA15-3 is another large transmembrane glycoprotein also termed *MUC1*. MUC1 is involved in metastasis in breast cancer.[12] Furthermore, CA15-3/MUC1 mediates transendothelial tumor cell migration by ligating endothelial intercellular adhesion molecule-1 (ICAM-1).[28] The role of carbohydrate antigen CAMs, including Lewis antigens, in RA-associated adhesive events has been elucidated.[29,30]

In this study, we assessed serum TAA levels in RA patients in comparison to healthy controls. In addition, TAA production in RA patients was correlated with laboratory markers of disease activity and outcome, such as RF, CRP, and anti-CCP.

PATIENTS AND METHODS

Patients and Controls

Altogether 75 RA patients were included in the study. The patient population contained 62 women and 13 men, their mean age was 50.1 ± 13.8 years (range: 38–75 years). The mean disease duration was 10.9 ± 8.6 years (range: 1–44 years). Fifty age- (mean age: 54.5 ± 9.3 years; range: 43–79 years) and sex-matched (41 women and 9 men) healthy blood donors served as controls. None of the RA patients or controls ever had any malignancies. Serum samples were obtained from all patients and controls. All sera were assayed for TAAs, while RA patient sera were also submitted for the determination of RF, CRP, and anti-CCP concentrations. Clinical activity of RA was determined by the calculation of Disease Activity Score (DAS28). Institutional Ethical Committee approval was obtained for this study.

Determination of Serum Tumor Antigen Concentrations

TAAs including CEA, CA19-9, CA15-3, CA125, CA72-4, and NSE were determined by electrochemiluminescence immunoassays using the Modular E170 automated analyzer (Roche, Basel, Switzerland), according to the manufacturer's instructions. The normal upper limit for these TAAs, determined by the manufacturer, was as follows: CEA 3.4 μg/L, CA19-9 34 kU/L, CA15-3 25 kU/L, CA125 35 kU/L, CA72-4 6.9 kU/L, and NSE 16.3 μg/L. All RA and normal sera were assayed for these TAAs, and the percentage of "positive"

patients (values above the upper limit), as well as the absolute values of serum concentrations was compared. In addition, absolute TAA concentrations in the sera of RA patients were correlated with the corresponding RF, CRP, and anti-CCP levels (see below). In correlation studies, patients with values above or below the upper or lower cutoff were excluded.

Determination of RF, CRP, and Anti-CCP Antibody

Serum IgM RF and CRP levels were assessed by quantitative nephelometry (Cobas Mira Plus; Roche, Basel, Switzerland), using RF and CRP reagents (Dialab, Budapest, Hungary). RF values >50 U/mL and CRP values ≥ 5 mg/L were regarded as positive. Anti-CCP autoantibodies were detected in serum samples using Immunoscan-RA CCP2 ELISA test (Eurodiagnostica, Arnhem, the Netherlands). The assay was performed according to the manufacturer's instructions. A serum concentration >25 U/mL was considered positive.

Statistical Analysis

The descriptive data of normally distributed variables are expressed as the mean $\pm$ SD. Statistical analysis was carried out by paired two-tailed *t*-test. Correlations between variables were determined using the Pearson correlation coefficient. *P*-values < 0.05 were considered significant.

RESULTS

Serum CA19-9, CA125, and CA15-3 Levels Are More Frequently Elevated in RA

When TAA concentrations were determined in the sera of RA patients and controls, significantly more RA patients exhibited abnormally high levels (values above the upper normal limit) of CA19-9 (8.1% of patients versus 0% of controls), CA125 (10.8% versus 7.1%), and CA15-3 (17.6% versus 14.3%) ($P < 0.05$). There were no statistically significant differences between RA patients and controls regarding the serum levels of CEA (22.2% versus 21.4%), CA72-4 (2.7% versus 2.1%), and NSE (23.0% versus 24.6%) (FIG. 1).

The Absolute Concentrations of CA19-9 and CA125 Are Higher in RA

The mean serum levels of CA19-9 (14.2 ± 1.2 versus 10.5 ± 1.6 kU/L) and CA125 (23.9 ± 1.8 versus 16.8 ± 2.2 kU/L) were also significantly higher in

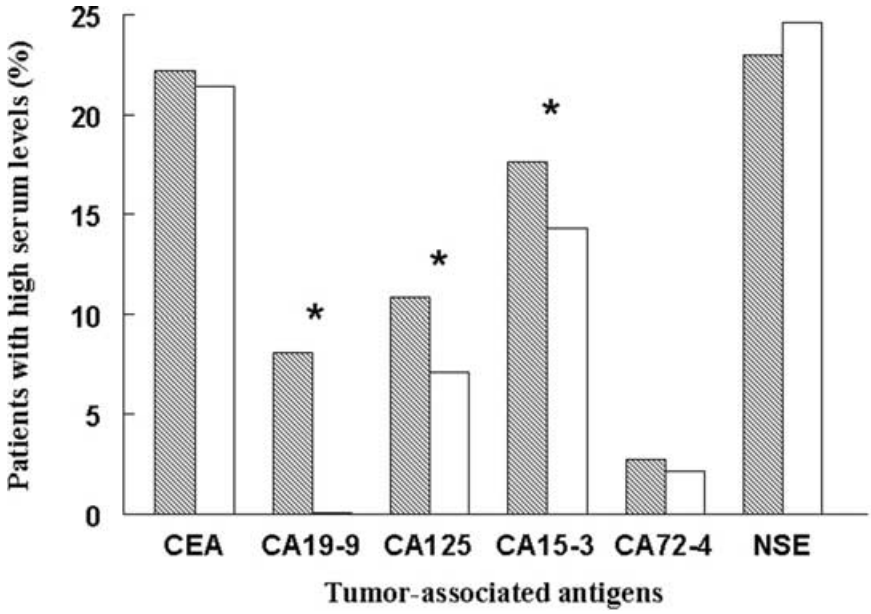

FIGURE 1. Percentage of RA patients and controls with elevated TAA serum levels (above upper normal limit). CA19-9, CA125, and CD15-3 concentrations were elevated in significantly more RA patients than healthy subjects. Asterisks indicate statistically significant differences ($P < 0.05$).

RA compared to controls ($P < 0.05$). There were no significant differences between RA patients and controls in serum CEA (1.8 ± 0.9 versus 2.6 ± 1.6 μg/L), CA15-3 (18.6 ± 3.3 versus 19.2 ± 5.3 kU/L), CA72-4 (2.5 ± 1.6 versus 1.5 ± 1.4 kU/L), and NSE (13.7 ± 4.5 versus 16.3 ± 7.8 μg/L) (FIG. 2).

Correlation between TAA Levels and Other Markers in RA

When serum concentrations of two distinct TAAs were correlated in the RA patients, CA125 showed significant correlation with CA15-3 ($r = 0.377$, $P < 0.05$) (FIG. 3).

Regarding laboratory markers of disease activity and/or prognosis, only serum CEA levels showed significant correlation with RF ($r = 0.270$; $P < 0.05$) (FIG. 4). In addition, RF levels also correlated with anti-CCP ($r = 0.275$, $P < 0.05$) (FIG. 5) and CRP production ($r = 0.473$, $P < 0.05$) (FIG. 6), but not with any TAAs (data not shown). None of the assessed TAAs showed any correlation with CRP, anti-CCP, DAS28, age, or disease duration (data not shown).

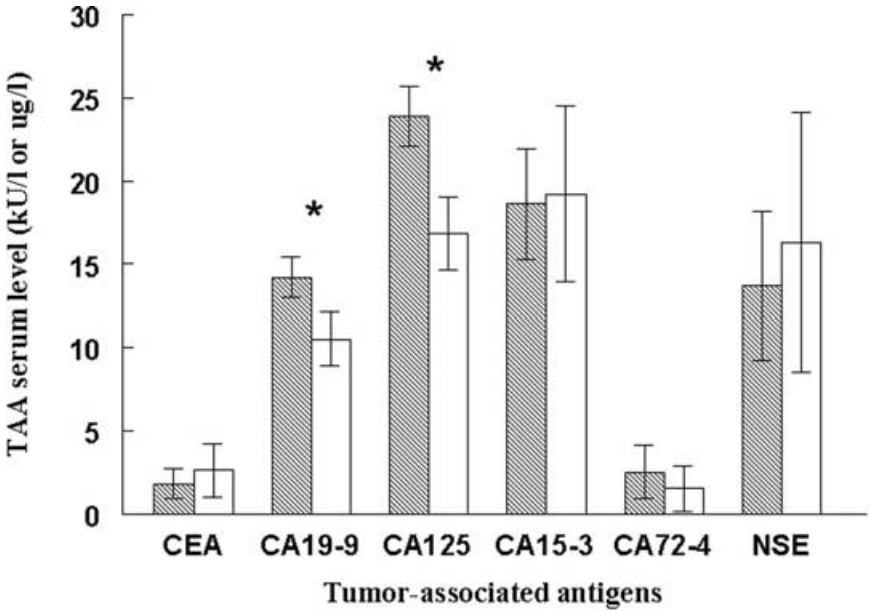

FIGURE 2. Mean TAA serum levels in RA patients and controls. The mean concentrations of CA19-9 and CA125 were higher in RA patients compared to controls. Asterisks indicate statistically significant differences ($P < 0.05$).

DISCUSSION

Apart from tumor cells, TAAs may be expressed by inflammatory leukocytes and, in soluble form, TAAs may be readily detected in the sera of cancer patients, as well as that of patients with various autoimmune inflammatory diseases.[10,19,21–26] In this study, we assessed serum levels of CEA, CA19-9, CA125, CA15-3, CA72-4, and NSE in 75 RA patients and 50 control subjects. All of these TAAs were readily detectable in most RA and control sera.

When investigating and comparing the percentage of RA patients and control subjects with elevated serum TAA levels (serum concentrations above the upper normal limit), significantly more RA patients were "TAA positive" for CA19-9 (8% versus 0%), CA125 (11% versus 7%), and CA15-3 (18% versus 14%) than healthy subjects. In addition, when mean serum levels were analyzed, the serum concentrations of CA19-9 (14 versus 10.5 kU/L) and CA125 (24 versus 17 kU/L) were also elevated in RA compared to controls. "TAA positivity" for or serum levels of CEA, CA72-4, and NSE were not different in the patients and controls. There is relatively little information available regarding soluble TAA production in RA. CA19-9 has been detected in the sera of RA, as well as SLE, SSc, SS, MCTD, and myositis patients.[10,22,26] However, the increased production of CA125 or CA15-3 in RA has not yet been confirmed.

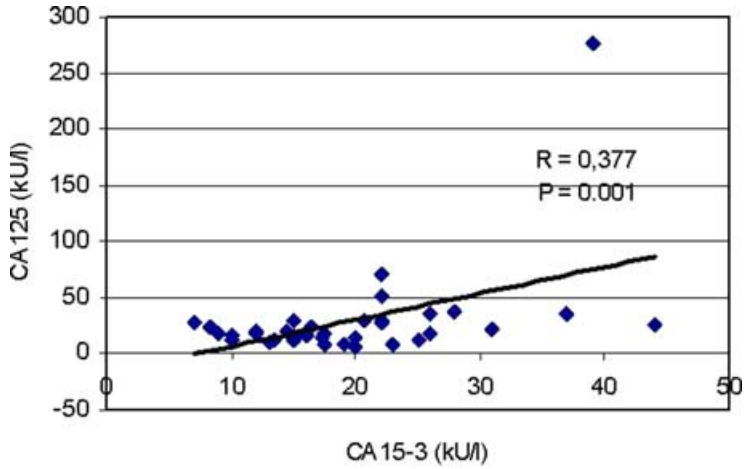

FIGURE 3. Significant correlation between serum CA125 and CA15-3 levels in RA patients ($P < 0.05$).

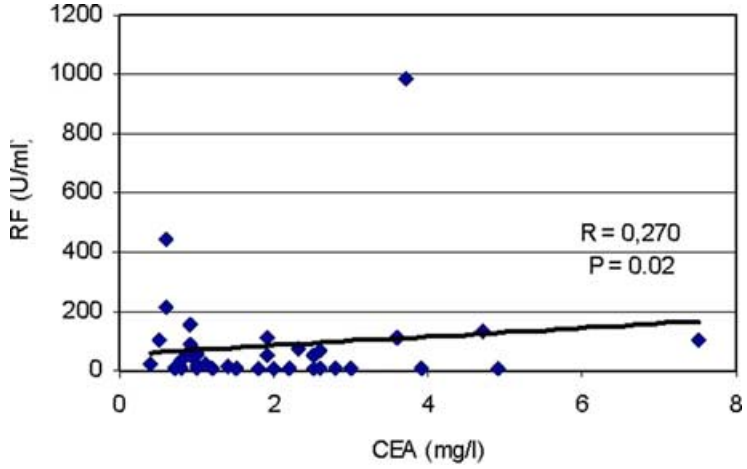

FIGURE 4. Significant correlation between serum RF and CEA concentrations in RA patients ($P < 0.05$).

Increased CA125 production has been associated with pleural effusion in SSc and SLE.[23,25] Serum levels of CA15-3 were elevated in SSc associated with severe pulmonary involvement.[24] We and others have previously detected the expression of CEA on synovial leukocytes in RA.[9,19,21] However, in this study, the increased production of soluble CEA in RA was not confirmed. In summary, CA19-9, CA125, and possibly CA15-3 production may be increased in RA compared to healthy subjects.

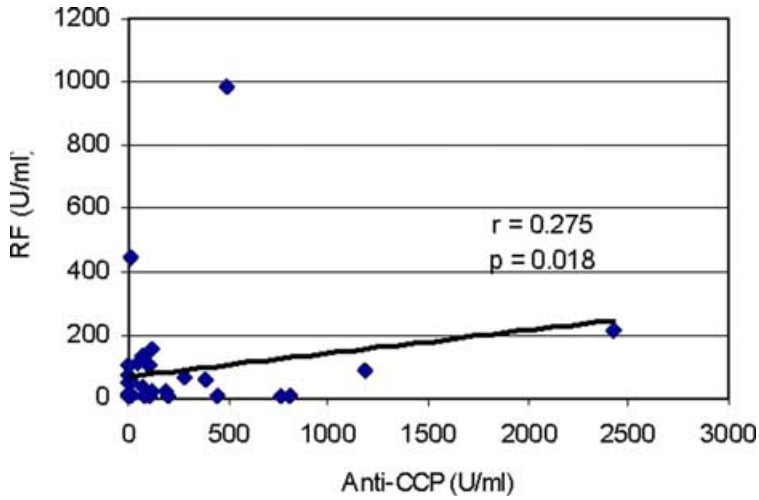

FIGURE 5. Significant correlation between serum RF and anti-CCP antibody levels in RA patients ($P < 0.05$).

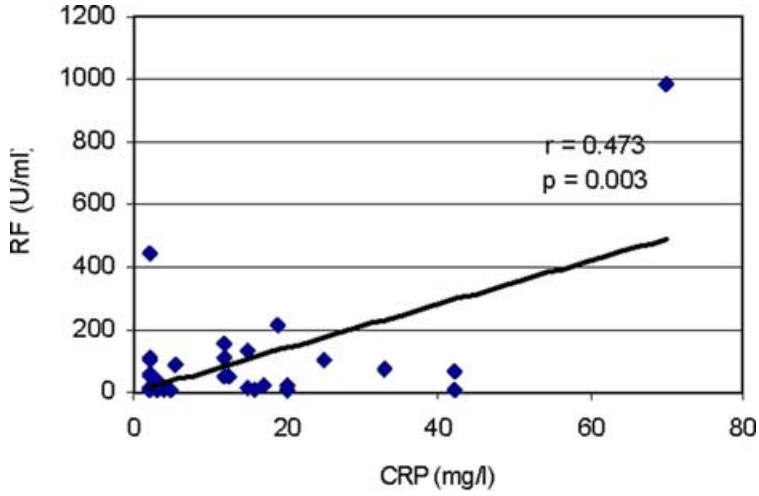

FIGURE 6. Significant correlation between serum RF and CRP levels in RA patients ($P < 0.05$).

When performing correlation analysis between any two TAAs, only serum CA125 and CA15-3 levels could be significantly correlated ($P < 0.05$). These data underscore the possible association of these two TAAs with RA. We have not found any other studies where serum levels of various soluble TAAs were correlated with each other in RA.

In order to search for possible disease activity and/or prognostic markers among the TAAs, serum TAA levels were correlated with serum concentrations of IgM RF, CRP, and anti-CCP antibodies, as well as with the clinical activity score DAS28. Only CEA levels showed significant correlation with RF production ($P < 0.05$). Although we could not detect elevated soluble CEA production in RA patients compared to healthy controls, soluble CEA is readily detectable in most RA sera, and previous studies showed synovial expression of cellular CEA.[9,19,21] In addition, in the early report by Unger *et al.*,[21] elevated plasma CEA levels were detected in seropositive, but not seronegative RA patients, which again underscores a possible association between CEA and RF production.

The exact pathogenic role of TAAs in RA remains to be elucidated. Among TAAs investigated in this study, CEA, CA19-9, CA125, and CA15-3, but not CA72-3 and NSE, contain carbohydrate motifs and exert adhesive properties during tumor metastasis formation. The CEA family (CD66a-CD66e antigens) belongs to the immunoglobulin superfamily of CAMs.[13] The CD66 antigens contain the oligosaccharides LeX and sLeX[16]; it has been postulated that neutrophils may use CD66 to bind to E-selectin expressed by activated endothelium.[15,19] Although in the present study we were unable to detect increased production of soluble CEA in RA, previous studies confirmed that there is abundant expression of CD66 and E-selectin in the RA synovium.[9,31] Here we also demonstrated significant positive correlation between CEA and RF production in RA. Thus, CEA may be involved in adhesive interactions underlying synovial inflammation.

In this study, we found increased production of CA19-9, CA125, and CA15-3, but not that of CA72-4 and NSE in RA. Interestingly, CA19-9, CA125, and CA15-3 have been associated with intercellular adhesion, but CA72-4 and NSE have not. These three TAAs, as well as CEA, contain carbohydrate motifs and have been implicated in adhesive events underlying tumor metastasis.[11,12,27,28,32,33] The immune determinant of CA19-9 is another Lewis antigen, sLe-a. sLe-a is also a ligand for the CAM E-selectin.[27] A correlation between CA19-9 and ICAM-1 production in inflammatory liver disease suggests that these two CAMs may be simultaneously overexpressed during inflammatory processes.[27] CA125, a giant mucin-like glycoprotein, also known as MUC16, mediates cell adhesion to mesothelin, a glycosylphosphatidylinositol-linked cell-surface molecule. Mesothelin is expressed in many tumor cells. The interaction of CA125/MUC16 and mesothelin is involved in the adhesion of ovarian cancer cells during metastasis formation.[11] CA125 also binds to galectin-1, a cell-surface lectin implicated in cell adhesion, proliferation, and apoptosis.[32] Finally, CA15-3 is also known as MUC1. CA15-3/MUC1 is the most widely used serum marker in breast cancer. This is a large transmembrane glycoprotein mediating cancer cell adhesion during metastasis.[12] It has been shown recently, that CA15-3/MUC1 ligates endothelial ICAM-1 and thus mediates transendothelial migration of tumor cells.[28] This

TAA has also been implicated in T cell migration and lymphocyte–endothelial adhesion in inflammation.[33] The role of Lewis antigens including Le-y in RA has been confirmed.[29,30] We have not found any reports regarding possible adhesive properties of CA72-4 or NSE. Thus, in this study, only TAAs acting as CAMs exerted abundant production in RA.

As secondary results, in this study we also confirmed that RF production is significantly correlated with serum anti-CCP and CRP levels ($P < 0.05$). RF is a prognostic marker, which has been correlated with unfavorable disease outcome. However, RF is not a disease activity marker. CRP is an activity marker, while anti-CCP levels have been associated with both disease activity and progression.[2–5] There is controversy regarding possible correlations between RF and anti-CCP production, as some investigators found positive correlation,[6,7] while others could not confirm this.[8]

In conclusion, some TAAs including CA19-9, CA125, and CA15-3, carbohydrate antigens with adhesive properties, exert increased production in RA. Thus, these TAAs may be involved in intercellular adhesion underlying synovial inflammation. Furthermore, the production of some TAAs, such as CEA, may correlate with serum RF concentrations suggesting that soluble TAA measurements may have prognostic relevance in RA.

ACKNOWLEDGMENTS

This work was supported by research grant T 048541 (Z.S.) from the National Foundation for Scientific Research (OTKA). We thank Ms. Erika Szakácsné Szilágyi for her expert technical assistance.

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