HUMAN HIV-1 TAT-INTERACTIVE PROTEIN 2 AS A PROGNOSTIC AND/OR DIAGNOSTIC FACTOR FOR ANKYLOSING SPONDYLITIS, RHEUMATOID ARTHRITIS AND SARCOIDOSIS

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ABSTRACT

***Introduction**: Some chronic inflammatory or autoimmune conditions and various cutaneous granulomatous disorders are associated with an increased occurrence of malignancies. Human HIV-1 TAT-Interactive Protein 2 (HTATIP2/TIP30), also called TIP30 or CC3, is expressed in human tissues and some tumor tissues. Therefore, HTATIP2/TIP30 can be a possible target for early diagnosis, prediction of prognosis, and/or treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS) and sarcoidosis co-morbid malignancies.*

***Materials and methods**: Erythrocyte sedimentation rate (ESR) (Westergren method), serum C-reactive protein (CRP), and rheumatoid factor (RF), levels were measured. The immunonephelometric method was used for measuring CRP and RF levels (BNII, Dade Behring, Germany). Human Hiv-1 TAT-Interactive Protein 2 (HTATIP2/TIP30) concentration was determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit.*

***Results**: This study evaluated serum HTATIP2/TIP30 levels in patients with RA, AS and sarcoidosis and healthy controls. There was no difference between serum HTATIP2/TIP30 levels of healthy controls, RA and sarcoidosis patients. However; the serum level of HTATIP2/TIP30 was significantly higher in AS patients than in healthy controls suggesting a potential target for early diagnosis, prediction of prognosis, and treatment of AS and AS related co-morbidities, but not for RA and sarcoidosis.*

***Conclusion**: This study demonstrated a potential role of HTATIP2/TIP30 in AS for the first time that enlightens future studies targeting HTATIP2/TIP30 in AS and other rheumatologic and inflammatory diseases.*

***Key words**: Ankylosing spondylitis, rheumatoid arthritis, sarcoidosis, HTATIP2/TIP30.*

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Introduction

Some, though not all[(1)], chronic inflammatory or autoimmune conditions are associated with an increased occurrence of malignancies[(2-4)]. The role of chronic inflammation in the development of cancer has been a topic of both epidemiological and experimental studies. In rheumatoid arthritis (RA), an increased risk of lymphoma has been reported[(5)]. Treatment with cytotoxic drugs has been linked to the development of specific cancers[(6)]. Chronic infection or persistent inflammation has been suggested as a driving force for de novo lymphogenesis, resulting in malignancy[(7)].

High inflammatory activity has been proposed as an independent risk factor for lymphomas in patients with RA[(8)]. In other organs, such as the lung and liver, chronic inflammation, sometimes in connection with fibrosis, is associated with malignant transformation[(9, 10)].

Ankylosing spondylitis (AS) is a chronic inflammatory joint disease in which the anatomical distribution of arthritis, the type of joint destruction, the extra-articular manifestations and the sex distribution (among other factors) differ from RA. Yet, information on the risk of malignancies in AS is surprisingly limited, but signals increased risks[(11, 12)]. Patients with AS and other rheumatological dis-

eases may have an increased incidence of malignancies, notably leukemia in AS, and non-Hodgkin's lymphoma and leukemia in rheumatoid arthritis (RA)[13]. In AS, the increased leukemia risk has been attributed to spinal irradiation[14].

In addition, various cutaneous granulomatous disorders have been found to be associated with internal malignancy. Among them, granuloma anulare, psoriasis, pyoderma gangrenosum, and sarcoidosis may precede the development of a neoplastic process by months or years[15-17]. In a majority of cases, sarcoidosis precedes malignancy, suggesting that an immune dysfunction secondary to sarcoidosis may facilitate tumorigenesis. Evidence is strongest for lymphoproliferative malignancies, myeloproliferative malignancies, and lung cancer; in an estimated 67-76 percent of cases these malignancies appear more than 12 months after the onset of sarcoidosis[18]. On the other hand, testicular and cervical cancers predominantly precede sarcoidosis, which may reflect the presence of different etiologies between these types of malignancies and others that demonstrate a reverse sequence between the onset of sarcoidosis and cancer[19].

All above data demonstrates that RA, AS and sarcoidosis are highly related with co-morbid cancer. Early diagnosis generally is not possible because there is a lack of noticeable signs or symptoms. For these reasons, co-morbid cancers are frequently diagnosed at an advanced stage. Thus, any improvement in early diagnosis, prediction of prognosis, and treatment is desirable.

Human HIV-1 TAT-Interactive Protein 2 (HTATIP2/TIP30), also called TIP30 or CC3, is an evolutionarily conserved gene that is expressed ubiquitously in human tissues and some tumor tissues. Human TIP30 was identified to be bound to the transcriptional activation domain of the human immunodeficiency virus (HIV-1) TAT and, was as a cofactor to specifically enhanced TAT-activated transcription[20]. The finding of roles for HTATIP2/TIP30 in apoptosis and tumor suppression, especially in control of expression of genes involved in apoptosis and metastasis suppression, indicates that there is a signal pathway facilitated by HTATIP2/TIP30 and its associated factors[21-26]. Therefore, HTATIP2/TIP30 can be a possible target for early diagnosis, prediction of prognosis, and/or treatment of co-morbid cancers. However to date there is no study investigating potential role of HTATIP2/TIP30 in RA, AS or sarcoidosis.

In the light of above data, this study aimed to investigate the levels of HTATIP2/TIP30 in patients with RA, AS and sarcoidosis using Enzyme-linked immunosorbent assay (ELISA) method and to determine whether altered HTATIP2/TIP30 levels correlate to any of these diseases.

Materials and methods

The study was conducted at the physical medicine and rehabilitation outpatient clinic of Ataturk university faculty of medicine. All the participants were informed of the study protocol and their written informed consents were obtained according to the Declaration of Helsinki.

20 patients with RA, 22 patients with AS, 15 patients with sarcoidosis, and 20 healthy controls from the same geographical area were consecutively included.

The patients with RA fulfilled the criteria of the American College of Rheumatology (ACR) for RA[27]. The patients with AS met modified New York criteria for AS[28].

A diagnosis of sarcoidosis was established in accordance with published criteria from the World Association of Sarcoidosis and Other Granulomatous Diseases (Statement on sarcoidosis)[29].

The patients had sarcoidosis determined by several symptoms such as acute respiratory illness, sweats, dyspnea, and dry cough, chest X-ray findings and lung function tests. 10 patients had history of arthritis.

The control group consisted of 20 healthy volunteers from a similar ethnic origin, without any evidence of disease.

All patients and healthy subjects were evaluated with a complete history, a clinical and laboratory examination. Patients having an overlap of RA, AS and sarcoidosis with other rheumatic diseases like systemic lupus erythematosus or systemic sclerosis were excluded from the study.

Blood sampling

Blood samples were collected from patients and healthy controls, and stored at-80 0C. We take venous blood from vena medina cubiti. We did not perform fasting before acquiring the blood.

Biochemical Analyses

Erythrocyte sedimentation rate (ESR) (Westergren method), serum C-reactive protein

(CRP), and rheumatoid factor (RF), levels were measured. The immunonephelometric method was used for measuring CRP and RF levels (BNII, Dade Behring, Germany). Human Hiv-1 TAT-Interactive Protein 2 (HTATIP2/TIP30) concentration was determined using a commercially available ELISA kit (Cusabio Bioteh Co.,Ltd. Catalog No: CSB-E14917H ELISA kit).

Statistical analyses

The statistical analysis was performed using Statistical analysis was performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). The values of measurable parameters were checked for normal distribution by means of the Kolmogorov-Smirnov test prior to statistical analysis. One-Way ANOVA and Tukey Posthoc tests were used for the statistical analysis. Values with $p < 0.05$ were considered statistically significant.

Results

The demographic, clinical, and laboratory characteristics of patients and healthy controls are shown in Table 1. 20 patients with RA (6 male and 14 female), 22 patients with AS (15 male and 7 female), 15 patients with sarcoidosis (9 male and 6 female), and 20 healthy controls (13 male and 7 female) were analyzed.

	RA n=20	AS n=22	Sarcoidosis n=15	Controls n=20	p1	p2	p3
Age (years)	**43.05±13.13***	35.5±10.26	37.73±11.66	32.7±9	ns	ns	ns
Disease duration (month)	102±94.21	95.64±48.5	**29.33±31.8*****	-	ns	<0.05	ns
ESR (mm/h)	27.55±16.21	32.41±25.58	13.53±7.51	13.99±9.6	ns	<0.01	<0.01
CRP (mg/l)	5.25±9.76	16.11±18.25	6.44±6.38	0.77±0.99	<0.05	ns	<0.001
RF	**44.01±38.4****	11.41±3.47	**13.17±5.44******	10.65±4.33	<0.001	ns	ns
TIP30 protein	1.86±1.25	4±4.87	1.55±0.7	1.4±0.45	ns	<0.05	<0.05

Table 1: The clinical and laboratory features of RA, AS and sarcoidosis patients and healthy controls.

**p< 0.05, ** p< 0.001: Significance between RA patients and healthy controls*

****p< 0.01, **** p< 0.001: Significance between RA and sarcoidosis patients*

P1: Significance between AS and RA patients

P2: Significance between AS and sarcoidosis patients

P3: Significance between AS patients and healthy controls.

The RA patients were older than healthy controls ($p<0.05$). In addition, disease duration of RA patients was longer than patients with AS ($p<0.05$) and sarcoidosis ($p<0.01$).

ESR levels in AS patients were significantly higher than in sarcoidosis patients and in healthy controls ($p<0.01$). Also, in patients with AS, serum CRP levels were significantly different than in patients with RA ($p<0.05$) and in healthy controls ($p<0.001$).

Serum TIP30 protein values were found in AS patients higher than those of patients with sarcoidosis ($p<0.05$), RA ($p= 0.059$) and healthy control ($p<0.05$).

Discussion

Irritable bowel syndrome is described as abdoClinical studies coping with status of HTATIP2/TIP30 expression in different diseases are limited. The aim of this study was to demonstrate the involvement of HTATIP2/TIP30 in RA, AS and sarcoidosis patients. Tat-interacting protein 30 (TIP30) is a transcriptional cofactor that functions as a metastasis suppressor via its ability to inhibit tumor growth[26] and angiogenesis[23, 25] and to induce apoptosis[21, 30] demonstrated that weak or negative expression of TIP30 contributed to the development and progression of gastric cancer. When TIP30 expression was silenced, spontaneous development of hepatocellular carcinoma and other tumors was observed in mice[22]. In contrast, ectopic expression of TIP30 elevates the expression of a subset of pro-apoptotic genes[21], which subsequently inhibit tumorigenesis in liver and lung. The direct involvement of TIP30 in cell proliferation and apoptosis gives it significant potential as targets of co-morbid cancers. Thus, identification apoptotic factors such as TIP30 in benign and malignant lesions of occurring in inflammatory and/or immune diseases such as RA, AS and sarcoidosis will be important for developing new diagnostic and even treatment strategies in co-morbid cancers related to AS, RA and sarcoidosis[31]. There have been numerous reports of an association between rheumatic diseases and the development of tumors. Several factors including the autoimmune disease itself, common etiology between the rheumatic disease and malignancy, including genetic factors, viruses (e.g. Epstein-Barr virus, retroviruses), smoking causing tissue necrosis, etc., have been implicated in the pathogenesis of tumor development. However, it is difficult to separate disease-related mechanisms from the potential oncogenic properties of immunosuppressive drugs used in these autoimmune-inflammatory

diseases[32-35]. It may be difficult to differentiate secondary malignancies developing in an autoimmune patient and musculoskeletal paraneoplasias (36). So in this study we evaluated TIP30 serum levels in patients with RA, AS and sarcoidosis patients by hypothesizing that TIP30, a proapoptotic factor, may be a potential prognostic and/or diagnostic factor for inflammatory and/or immune diseases related secondary malignancies.

The association of malignant tumors with RA has been extensively examined in observational studies for the past 40 years, and is identified as serious adverse effects in clinical trials of new therapeutic agents for RA[37]. Several investigators found an increased risk for the development of lymphoproliferative disorders and lung cancer, but a decreased risk for the development of colorectal malignancies in RA[34, 38]. High long-term inflammatory activity in RA seems to have been associated with increased tumor risk[36]. In addition, cancer risk in RA may also be related to age and long-lasting disease. In large recent cohorts, the risk of lymphoma in RA patients was higher than in the general population[34, 38]. Also, B cell stimulation caused by chronic Epstein-Barr virus infection may be a pathogenic factor in RA-, as well as Sjögren's Syndrome -associated lymphoma[34, 35]. Smoking may be an important pathogenic factor in RA-associated lung cancer, as well as in RA itself (39). In our study we evaluated serum levels of TAT30 in RA patients and healthy controls and determined that there is no significant difference between RA patients and healthy volunteers.

Sarcoidosis, a chronic idiopathic systemic disease characterized by infiltration with non-caseating granulomas, has been observed in association with various entities, ranging from autoimmune disorders, Crohn disease, celiac disease, and amyloidosis, but its association with internal malignancies has been a particular focus of intense investigation[40]. Cases of sarcoidosis diagnosed before, concomitant with, and after the detection of cancer are well documented in the literature, but the precise nature and strength of this association remains controversial. Whereas the association between sarcoidosis and malignancy is well documented, the mechanisms explaining these observations remain undetermined[19, 41].

Several theories related to immune dysregulation, impairment of cellular immunity, and other sequelae of chronic inflammation have been proposed[19]. In this study we investigated the possible role of TAT30 protein in sarcoidosis. There was no difference of TAT30 between the serum levels of patients with sarcoidosis and healthy volunteers. So future studies targeting new different diagnostic factors for sarcoidosis will need to be tailored against the cellular pathways that also favor the development of cancers[42].

Ankylosing spondylitis (AS) is a chronic inflammatory joint disease that can lead to chronic pain in axial and peripheral joints and to functional impairments after several years. Excess mortality has been reported in patients with AS. As it is known, low apoptosis and disordered polarization of peripheral blood T cells in might involve in the immunopathogenesis of AS[43] TIP30 is a normal cellular protein originally identified as a tumor suppressor that, when present in excess, blocks nuclear import[44, 45]. It is known to be upregulated by heat shock, stress, aging, certain viruses, and the cytokine transforming growth factor β. The tumor-suppressive activity of TIP30 has been linked to the induction of apoptosis, possibly by blocking of nuclear pores[44] and the suppression of osteopontin[46] a proinflammatory cytokine that has been implicated in the generation of Th17 cells, important for the generation of cell-mediated immunity. In our study TAT30 serum levels of AS patients were significantly higher than that of healthy volunteers. The increase in TAT30 in serum levels of patients with AS may be related with secondary diseases and mortality. TAT30 may have been increased in response to low apoptosis in AS patients. So the increase in TAT30 protein may be a prognostic and/or diagnostic indicator for severity of disease and/or related co-morbid cancers in patients with AS.

Conclusion

We demonstrated that serum HTATIP2/TIP30 protein levels may be a potential target for early diagnosis, prediction of prognosis, and treatment of AS and AS related co-morbidities, but not for RA and sarcoidosis. At clinical level, our study is not enough to suggest whether HTATIP2/TIP30 tissue expression is involved at onset of AS co-morbid malignancies. So, future clinical and experimental studies are required to display conclusive role of HTATIP2/TIP30 in secondary cancers related to AS. This study demonstrated a potential role of HTATIP2/TIP30 in AS for the first time that enlightens future studies targeting HTATIP2/TIP30 in AS and other rheumatologic and inflammatory diseases and related malignancies.

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