Serum and synovial survivin in rheumatoid arthritis: Relation to disease activity and severity

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Background
Rheumatoid arthritis (RA) is a progressive debilitating autoimmune disease, affecting 1% of the world population, leading to cartilage and bone destruction caused by insufficient apoptosis in the inflamed RA synovium. Survivin is a proto-oncogene biomarker known for its anti-apoptotic and cell cycle-regulating properties. Overexpression of survivin in non-cancerous processes has been linked to inflammation, presumably contributing to the decreased apoptosis in the T cells of the cerebrospinal fluid in multiple sclerosis, in skin lesions of patients with psoriasis and in synovial tissue of patients with RA.

Aim of the work
The aim of this study is to measure the serum and synovial levels of survivin and clarify their relations to disease activity, functional capacity, and radiographic damage in patients with RA.

Patients and methods
This study was carried out on 50 patients with RA who had a mean age of 46.4±10.94 years. They were 39 females and 11 males. The control group was of matched age and sex, with a mean age of 46.03±10.53 years and female : male ratio of 23 : 7. All patients were subjected to full history taking, thorough clinical examination, assessment of disease activity by disease activity score 28 activity score, and assessment of functional capacity and disability using Health Assessment Questionnaire. Plain radiographs of both hands of feet were done, scored and graded by Larsen score. Serum survivin from all the studied participants and survivin levels in the synovial fluid aspirated from 18 patients with RA who presented with knee effusion at the time of examination were measured by enzyme-linked immunosorbent assay, using a pair of matched anti bodies (R&D systems, Abingdon, Uk).

Results
The mean serum survivin level was highly statistically significantly elevated ($P<0.001$) in the sera of patients with RA than in the controls, being 239.1 ±115.15 and 77.03±30.20 pg/ml, respectively. Synovial survivin levels ranged between 420 and 575 pg/ml, with a mean of 479.61±52.68 pg/ml, which was statistically significantly higher than the mean serum survivin level in patients with RA ($P<0.001$). Patients were divided into survivin –ve group, which included 21 (42%) of 50 patients with serum survivin less than 167.63 pg/ml, and survivin +ve group, which included 29 (58%) of 50 patients with RA with serum survivin more than or equal to 167.63 pg/ml. Survivin +ve RA patients group had significantly longer mean disease duration ($P<0.001$), Higher Health Assessment Questionnaire SCORE, and higher mean Larsen score ($P<0.001$) than survivin –ve RA patients group. Overall, nine (69.2%) of 13 RA patients with Sjogren's syndrome, eight (80%) of 10 of the patients with pleural effusion, three (50%) of six patients with Raynaud's phenomenon, and all patients with SC nodules (five, 100%), episcleritis (two, 100%), and vasculitis (one, 100%) were survivin +ve. Larsen score in the patients with RA ranged from 0 to 65, with a mean of 23.6 ±18.98. Patients with RA who had Larsen score grading more than or equal to 2 (27/50, 52%) were considered to have an erosive RA disease. There were no statistically significant differences between patients with RA according to the presence of erosion regarding age, sex, visual analog scale values, disease activity score values, the presence of rheumatoid factor antibodies or anti-cyclic citrullinated peptides antibodies, the mean of hemoglobin %, white blood cells count, platelets count, erythrocyte sedimentation rate first hour value, or the C-reactive protein level. All patients with RA with erosive disease were survivin +ve and had statistically significantly elevated mean serum and synovial survivin levels than those patients with non erosive disease (337.37±55.19 vs. 126.78±24.33 pg/ml and 422.5±3.53 vs. 486.75±51.52 pg/ml, respectively).

Conclusions
High levels of survivin are detected in the sera and synovial fluid of patients with RA and are associated with erosive joint damage and poor functional outcomes. Our findings support the role of survivin in the pathogenesis of RA. Further studies are needed on a larger group of RA patients follow-up to ascertain the erosive effect of survivin. Conduction of studies on survivin antagonist to evaluate their effect on ameliorating RA disease progression is recommended.

Keywords:
disease activity, erosion, rheumatoid arthritis, serum, synovial surviving

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Introduction

Rheumatoid arthritis (RA) is a progressive debilitating autoimmune disease, affecting 1% of the world population, leading to cartilage and bone destruction caused by insufficient apoptosis in the inflamed RA synovium. Recent treatment has been revolutionized by the use of biologic therapies, such as drugs that target cytokines, cells, and signaling pathways [1,2].

Survivin is a proto-oncogene biomarker of cancer and may be found in most tumor tissues, such as lymphoma, colorectal carcinoma, breast cancer, and small cell and lung adenocarcinoma, where it predicts prognosis and the potential for metastasis [3]. Survivin is known for its anti-apoptotic function in the cytoplasmic and mitochondrial compartments by preventing activation of caspases and cell cycle-regulating properties by aiding formation of a chromosomal passenger complex [4].

In healthy tissues, survivin expression is responsible for cell renewal and differentiation, being consistently expressed in thymocytes, bone marrow hematopoietic progenitors and stem cells, cells of the colon epithelium, and vascular endothelial cells [5].

Overexpression of survivin in noncancerous processes has been linked to inflammation, presumably contributing to decreased apoptosis in the T cells of cerebrospinal fluid in multiple sclerosis, in skin lesions of patients with psoriasis, and in synovial tissue of patients with RA [6].

In RA, survivin has abilities to inhibit apoptosis, promote cell proliferation, produce cytokines and growth factors, and promote the transformation of synovial fibroblasts to an invasive phenotype, followed by the proliferation of synovial tissue and pannus formation [1].

It is overexpressed in the preclinical phase of RA, and together with antibodies to citrullinated peptides, is predictive for development of RA several years ahead of clinical symptoms [7]. In the presymptomatic stage of RA, survivin was associated with the pattern of regulatory cytokines [interleukin (IL)-12, IL-1, IL-9, granulocyte-macrophage colony-stimulating factor, and IL-2], controlling the formation of pathogenic T helper (Th) 1 and Th17 lymphocytes [8].

Survivin is critical for the process of antigen presentation, the breaking point of immune responses in RA, being required for the expression of major histocompatibility complex class II molecule receptors on dendritic cells and for the formation of functional T cell receptors, and has been connected to the carriage of the human leukocyte antigen DRB1 genotype and smoking, important keystones in the pathogenesis of RA [9–13].

Expression of survivin in B cells might cause adverse cell recognition in RA, as changes in survivin expression after therapeutic B cell depletion was associated with a reduction of B cell numbers, serum levels of rheumatoid factor (RF), and the activity of arthritis [6].

It has recently emerged as a biomarker of RA. High levels of survivin are associated with severe joint damage and poor treatment response [13].

Patients and methods

This study was carried out on 50 patients with RA attending the outpatient clinic and the inpatient department of Rheumatology, Rehabilitation and Physical Medicine of Benha University Hospitals. All of them met the updated American College of Rheumatology/European League Against Rheumatism criteria for the classification of RA [14].

Another 30 apparently healthy volunteers with a comparable age and sex were included as a control group. Verbal consent was taken from all participants included in the study, and it was approved by the

Ethical Committee of Faculty of Medicine of Benha University on 6/2016.

(1) All patients were subjected to full history taking, thorough clinical examination, laboratory investigation, assessment of disease activity by disease activity score (DAS) 28 [15], and assessment of functional capacity and disability using Health Assessment Questionnaire (HAQ) [16]. Erythrocyte sedimentation rate was assessed by Westergren method, C-reactive protein (CRP) by latex agglutination slide test for qualitative and semiquantitative determination of CRP in nondiluted serum, RF by latex fixation test, and anti-citrullinated peptide antibody detected by enzyme-linked immunosorbent assay (ELISA).
(2) Serum and synovial survivin levels were measured by enzyme-linked immunosorbent assay by using a pair of matched antibodies (R&D Systems, Abingdon, UK). Values of circulating survivin above 167.63 pg/ml, corresponding to 3 SD of a healthy control group, were defined as positive.
(3) Radiological assessment: plain radiographs of both hands (P-A) and (A-P) of feet were done. The presence of erosion was classified as an erosive disease and scored by Larsen score [17].

Statistical analysis

Using the computer program SPSS (statistical package for social science) version 16, the collected data were summarized in terms of mean±SD and range for quantitative data and frequency and percentage for qualitative data. Comparisons between the different study groups were carried out using the χ^2 test and Fisher exact test to compare proportions as appropriate. The Student *t* test was used to detect mean difference between two groups regarding parametric data, whereas the Mann–Whitney test (*z*) was used to compare nonparametric data.

Results

This study included 50 patients with RA, who had a mean age of 46.4±10.94 years, comprising 39 females and 11 males, and 30 apparently healthy participant of matched age and sex to the patients, as a control group, with a mean age of 46.03±10.53 years, comprising 23 females and 7 males. The clinical and laboratory variables of the patients with RA are shown in Tables 1 and 2.

Overall, 42/50 (84.5%) of the patients with RA, whereas 8/30 (2.6%) of the controls were positive for RF. Moreover, 12/50 (24%) of the patients with RA had anti-cyclic citrullinated peptides (CCP) antibodies while all controls were negative for anti-CCP antibodies.

Table 1 The clinical characteristics of the patients with rheumatoid arthritis

Variable	Mean±SD	Range
Disease duration (years)	9.1±7.36	0.16–25
VAS (0–10 cm)	4.63±1.38	2–7
DAS28	5.11±0.9	3.28–7.19
HAQ score (0–3)	1±1.08	0–3
Locomotor system		
Duration of morning stiffness (h)	1.42±0.94	0.5–5
Number of tender joints	12±6	3–28
Number of swollen joints	2±3	0–14
Extra-articular manifestations [*n* (%)]		
Pleural effusion	10 (20)	
SC nodule	5 (10)	
Scleritis and episcleritis	2 (4)	
Sjogren syndrome	13 (26)	
Raynaud syndrome	6 (12)	
Vasculitis	1 (2)	
Disease activity		
Moderate	26 (52)	
Severe	24 (48)	

DAS28, 28-joint disease activity score; HAQ, Health Assessment Questionnaire; VAS, visual analog scale of pain.

Table 2 The laboratory characteristics of patients with rheumatoid arthritis

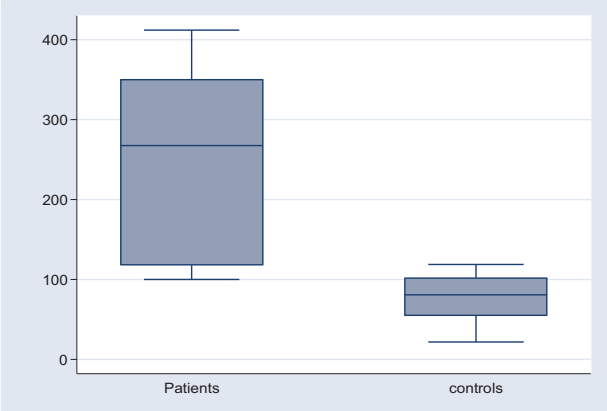
Variables	Mean±SD	Range
Hb (g/dl)	11.46±1.35	8.3–14
Leukocytes (cell/ mcl)	7.91±2.74	3.6–15.5
PLTs/mcl	304 733.3±117 751.9	170 000–571 000
ESR (mm/1st h)	66.17±28.22	0–120
CRP (mg/dl)	31.07±22.71	6–96

CCP, cyclic citrullinated peptides; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; PLTs, platelet count.

All patients with RA were on 200–400 mg/d hydroxychloroquine and weekly methotrexate injection (15.9±2.01/w), 35 patients were on oral prednisolone therapy (7.6±2.6 mg/dl), six patients were on 20 mg leflunomide, and two patients were on sulphasalazine (1.8±0.3 gm/d).

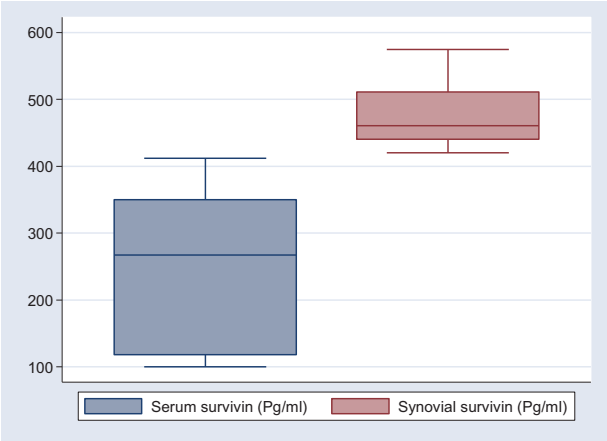
The mean serum survivin level was highly statistically significantly elevated ($P<0.001$) in the sera of the patients with RA than in the controls, being 239.1 ±115.15 and 77.03±30.20 pg/ml, respectively. Synovial survivin levels were measured in the synovial fluid aspirated from 18 patients with RA who presented with knee effusion at the time of examination and ranged between 420 and 575 pg/ml, with a mean of 479.61±52.68 pg/ml, which was highly statistically significantly elevated than the mean serum survivin level in the patients with RA (Figs 1 and 2).

Figure 1



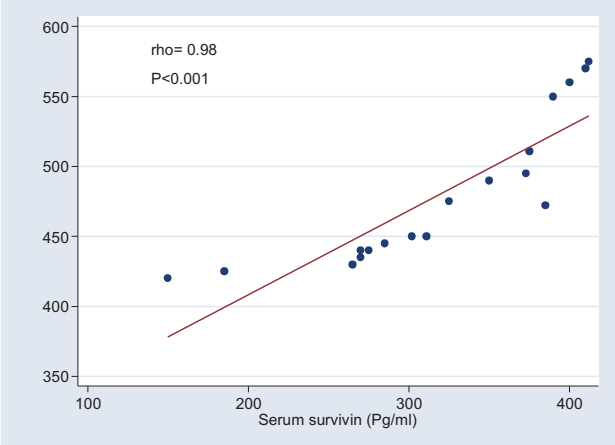
Comparison between mean serum survivin in the studied groups.

Figure 2



Comparison between mean serum and synovial surviving levels in the patients with RA group. RA, rheumatoid arthritis.

Figure 3



Both serum and synovial survivin levels were significantly positively correlated in the patients with RA group. RA, rheumatoid arthritis.

Both serum and synovial survivin levels were significantly positively correlated with disease duration (r=0.8, P<0.001 and r=0.61, P<0.008), HAQ scores (r=0.93, P<0.001 and r=0.94, P<0.001), and total Larsen scores (r=0.96, P<0.001 and r=0.99, P<0.001). Serum survivin levels were highly statistically positively correlated with the synovial survivin levels (r=0.98, P<0.001) (Fig. 3).

Patients were divided into two groups according to the serum survivin cutoff level, which was selected at the mean plus 3 SD for the control group .Survivin –ve group included 21 (42%) patients with RA with serum survivin level less than 167.63 pg/ml and survivin +ve group included 29 (58%) patients with RA with serum survivin level more than or equal to 167.63 pg/ml. Personal, clinical, and laboratory finding of the two groups are summarized in Table 3.

Survivin +ve patient group has significantly longer mean disease duration (P<0.001), higher mean HAQ scores, and higher mean Larsen scores (P<0.001) than survivin –ve patient group.

Overall, 9/13 (69.2%) of the patients with RA with Sjogren's syndrome, 8/10 (80%) of the patients with pleural effusion, 3/6 (50%) patients with Raynaud's phenomenon, and all patients with SC nodules (5, 100%), episcleritis (2, 100%), and vasculitis (1, 100%) were survivin +ve.

Larsen scores of the patients with RA ranged from 0 to 65, with a mean of 23.6±18.98. Patients with RA who had Larsen score grading more than or equal to two (27 (52%) of 50 patients) were considered to have an erosive RA disease. All patients with RA with erosive disease (27) were survivin +ve, whereas no one of the survivin –ve group patients had an erosive disease. Patients with RA with erosive disease has statistically significantly elevated mean serum and synovial survivin values than the patients with RA with nonerosive disease (P=0.03 and P<0.001) (Table 4).

There were no statistically significant differences between patients with erosive and nonerosive RA groups regarding age, sex, VAS values, DAS values, the presence of RF antibodies, anti-CCP antibodies, mean hemoglobin %, leukocytic count, platelets count, erythrocyte sedimentation rate first hour values, or CRP levels.

Discussion

Survivin is expressed in active rheumatoid synovium. Its expression was confirmed histologically in the

Table 3 Demographic, clinical, and laboratory characteristic of the patients with rheumatoid arthritis according to the serum survivin level

Variables	Survivin negative (<167.63 pg/ml) (*N*=21, 2%) [*n* (%)]		Survivin positive (≥167.63 pg/ml) (*N*=29, 58%) [*n* (%)]		Test	*P*
Sex						
Females	21 (100.0)		18 (62.1)		FET	0.24
Males	0 (0.0)		11 (37.9)			
Age (years) (mean±SD)	47±12.16	20–63	45.94±10.27	32–67	*t*=0.26	0.80
Disease duration (years) (mean ±SD)	3.38±2.91	0.16–9	13.47±6.7	5–25	*t*=4.05	<0.001 (HS)
VAS	5.08±1.11	3–7	4.29±1.49	2–6	*t*=1.58	0.12
DAS28	5.15±0.74	4.18–6.86	5.07±1.03	3.28–7.19	*t*=0.25	0.80
HAQ score	0±0	0	1.76±0.83	0–3	*t*=4.65	<0.001 (HS)
Disease activity						
Moderate	11	52.38	15	51.72	χ^2=0.002	0.96
Severe	10	47.62	14	48.27		
Locomotor system						
Duration of morning stiffness (h)	1.27±0.69	0.5–3	1.53±1.1	0.5–5	*t*=0.50	0.62
Number of tender joints	11.54±4.54	5–18	12.7	3–28	*t*=0.45	0.65
Number of swollen joints	2±3.44	0–12	2.59±3.32	0–14	*t*=1.36	0.17
Duration of treatment (years)	1.6±1.55	0.02–5	3.97±4.49	0.02–17	*t*=1.61	0.11
Erosion	0 (0.0)		27 (93.10)		χ^2=26.22	<0.001 (HS)
Total Larsen score (mean±SD)	6.54±6.79	0–18	36.65±14.19	19–65	*t*=7.04	<0.001 (HS)
Variable	Survivin negative (<167.63 pg/ml) (*N*=21)		Survivin positive (≥167.63 pg/ml) (*N*=29)		Test	*P*
	Mean±SD	Range	Mean±D	Range		
Hb (g/dl)	11.23±1.44	8.3–13.9	11.63±1.29	9.4–14	*t*=0.80	0.43
Leukocytes (cell/mcl)	8.01±2.93	3.8–15.5	7.83±2.67	3.6–14.1	*t*=0.17	0.86
PLTs/mcl	288 153.8±107 615.7	180 000–545 000	317 411.8±126 693.6	170 000–571 000	*t*=0.54	0.59
ESR (mm/h)	62.69±35.58	0–120	68.82±21.83	25–110	*t*=0.58	0.56
CRP (mg/dl)	29.31±24.25	6–96	32.41±22.12	6–96	*t*=0.6	0.54
Synovial survivin (pg/ml)	420 (*N*=1)	420	483.12±52.09 (*N*=17)	425–575	*t*=1.64	0.10

CRP, C-reactive protein; DAS28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate; FET, Fisher exact test; HAQ, Health Assessment Questionnaire; Hb, hemoglobin; HS, highly significant difference (P<0.001); PLT, platelet. Significant difference (P<0.05).

Table 4 Comparison between the mean serum and synovial survivin levels in patients with erosive and nonerosive rheumatoid arthritis

Variable	Nonerosive RA (*n*,%=23, 46%)		Erosive RA (*n*, %=27, 52%)		Test	*P*
	Mean±SD	Range	Mean±SD	Range		
Serum survivin (pg/ml)	126.78±24.33	100–185	337.37±55.19	265–412	*t*=4.66	<0.001 (HS)
Synovial survivin (pg/ml)	425±7.07 (*n*=2)	420–430	486.44±51.9 (*n*=16)	425–575	*t*=2.11	0.03 (S)

HS, highly significant difference (P<0.001); S, significant difference (P<0.05); *t*, Student's *t* test.

synovial tissues of patients with RA and was observed in the synovial tissue of collagen-induced arthritis animal model [18]. Considering that increased cell proliferation and resistance to apoptosis contribute to increased numbers of fibroblast-like synoviocytes and chronic inflammatory cells in rheumatoid joints, survivin has important implications for the pathogenesis of RA [19].

This study showed that the mean serum survivin levels were significantly elevated (P<0.00) in the patients with RA compared with the healthy controls, being 239.1±115.15 and 77.03±30.20 pg/ml, respectively, and synovial survivin levels ranged between 420 and 575 pg/ml, with a mean of 479.61±52.68 pg/ml, which was statistically significantly higher than the mean serum survivin level in the patients with RA

($P<0.001$). There was a positive relation between both serum and synovial levels.

This is consistent with previous observations found by Mahfouz *et al.* [20], who concluded that the mean serum survivin level for the RA group (335.0±119.3 pg/ml) was significantly higher ($P<0.0000$) than that for the controls (161.0±55.2 pg/ml), and it is close to that reported by Bokarewa *et al.* [21] who reported a survivin level of 121±2 pg/ml for the healthy individuals and a mean of 330±123 pg/ml in the RA group. Survivin is involved in many physiologic and pathologic steps in cellular response, metabolism, apoptosis, and cell cycle control [22]. Suppression of apoptosis has been suggested as a key mechanism supporting selection and accumulation of distinct lymphocyte subsets in chronically inflamed joint tissues [23]. Synovial T-cells in RA are highly differentiated and are not expected to survive for prolonged time within inflamed joints unless their death is actively inhibited [24].

The source of extracellular survivin in RA is not precisely identified. Possible sources include synovium itself, infiltrating cells in the synovial fluid, or circulating cells, such as leukocytes [22]. Bone marrow may be another potential source of survivin considering the fact that most of mononuclear cells of the peripheral blood continuously express survivin [21].

We found that survivin +ve patients with RA group has significantly longer mean disease duration ($P<0.001$), higher HAQ, and higher mean Larsen score ($P<0.001$) than survivin –ve patients with RA group.

All patients with RA with erosive disease were survivin +ve and had statistically significantly elevated mean serum and synovial survivin levels than those patients with nonerosive disease.

Previous studies reported by Ahn *et al.* [22] and others found that patients with erosive RA showed higher levels of synovial fluid survivin than patients with nonerosive RA, and the level of survivin was related to radiologic Larsen scores and the severity of chronic inflammatory arthritis.

Bokarewa *et al.* [21] found a significant association of survivin with the tendency of erosion of the joint and concluded that patients with RA with high levels of survivin had a risk of joint destruction 16 times higher, compared with those with low levels of survivin.

High levels of survivin were reported in a cross-sectional study of patients with juvenile RA and were associated with polyarticular and systemic onset of juvenile idiopathic arthritis (JIA) as well as with the active phase of the joint disease. This is of importance as the polyarticular/systemic type of arthritis and the inflammatory activity of JIA are important unfavorable prognostic parameters [25].

Apoptosis is a physiological process that mediates the programmed cell death controlling the regeneration of the tissues. Chronic inflammation in the joints is associated with an impaired apoptotic elimination of activated and autoreactive cells, resulting in hypertrophy of the inflamed synovia and the accumulation of inflammatory cells [26].

The results from the study conducted by Park *et al.* [27], provided evidence that survivin may promote synovial proliferation by stimulating angiogenesis.

The results by Chen *et al.* [1] showed that survivin helps the tumor-like proliferation of RA-fibroblast-like synoviocytes and is involved in the secretion of the proinflammatory cytokine IL-6 and MMPs. IL-6 promotes B-cell growth and differentiation, Th17 cell generation, and osteoclast formation [28]. MMP-9 was shown to be involved in the angiogenesis and the pannus formation in RA and to play pivotal roles in the development of synovial hyperplasia, sustained inflammation, and joint destruction, which has been considered as essential events in the development of RA [29].

On the contrary, in agreement with Ihn *et al.* [22], we did not find significant correlation between serum or synovial survivin in the patients with RA and disease activity assessed with DAS28, as DAS28 reflects the disease activity of RA at the systemic level rather than at the local joint level.Our results confirmed the results of Xing *et al.* [10], Bokarewa *et al.* [21], and Baran *et al* [30], who found a lack of direct correlation between serum survivin and inflammatory markers, including CRP and IL-6, which suggests a TNF-independent mechanism of survivin release.

This lack of correlation between survivin and inflammation was explained by Galeotti *et al.* [25] as it may be owing to different physiological mechanisms regulating survivin expression or owing to the different tissue origin of these proteins.

The nature of extracellular survivin release remains an enigma [31]. Active extracellular transport of survivin

is described only as exosomal content [2]. Profound cellular disruption could be a cause of intermittent serum levels of survivin. Extracellular survivin has been shown to be biologically active, inducing surface expression of adhesion molecules on leukocytes of patients with RA [32], with a potential to regulate T-cell functions and motility through a broad net of intracellular effectors [33]. At the preclinical stage of arthritis, serum survivin has been associated with the release of cytokines controlling the formation of Th cell subsets Th1 and Th17 [8]. Inhibition of survivin in experimental arthritis proved its intimate relation to the formation of effector T cells and to the system of matrix proteases in the inflamed joints [2]. The processes triggering and abrogating survivin release in RA could therefore pave a way to efficient therapeutic control of the disease.

Conclusion

High levels of survivin are detected in the sera and synovial fluid of patients with RA and are associated with erosive joint damage and poor functional outcomes. Our findings support the role of survivin in the pathogenesis of RA. Further studies are needed on a larger group of patients with RA with follow-up to ascertain the erosive effect of survivin. Conduction of studies on survivin antagonist to evaluate their effect on ameliorating RA disease progression is recommended.

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Conflicts of interest

There are no conflicts of interest.

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