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Collagen triple helix repeat containing 1 (CTHRC1) protein: A promising biomarker for evaluation of rheumatoid arthritis patients

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ABSTRACT

Aim of the work: To assess serum collagen triple helix repeat containing 1 (CTHRC1) protein level in rheumatoid arthritis (RA) patients and compare it with healthy controls. In addition, to evaluate the relation of its level with RA activity and severity

Patients and methods: The study included 60 adult RA patients and 60 matched controls. Disease activity score (DAS28), modified health assessment questionnaire (MHAQ) and RA medical records-based index of severity (RARBIS) were assessed in RA patients. Serum CTHRC1 levels were measured in patients and controls by enzyme linked immunosorbent assay (ELISA)

Results: They were 49 females and 11 males patients with a mean age of 43.6 ± 10.8 years and disease duration of 8.8 ± 0.9 years. The mean of DAS28 was 4.9 ± 2 (1.95–8.6). Serum CTHRC1 levels were significantly higher in patients than controls (1009.5 ± 79.4 vs. 470.7 ± 8.2 ng/ml, $p < 0.001$).The optimum cut-off value of CTHRC1 to discriminate patients from control was > 583.5 ng/ml with sensitivity of 98.3% and specificity of 100%. CTHRC1 significantly correlated with DAS28 ($r = 0.81$, $p < 0.001$), MHAQ ($r = 0.14$, $p = 0.002$), RARBIS ($r = 0.41$, $p = 0.006$), erythrocyte sedimentation rate (ESR) ($r = 0.57$, $p < 0.001$), C-reactive protein (CRP) ($r = 0.41$, $p = 0.002$), rheumatoid factor (RF) ($r = 0.31$, $p = 0.037$) and anti-cyclic citrullinated peptide (anti-CCP) ($r = 0.27$, $p = 0.036$). The significant predictors of increase CTHRC1 among patients were elevation in DAS28 (ß=287.6; $p = 0.007$, CI = 83.4–491.9) and MHAQ (ß=369.7; $p = 0.042$, CI = 14.5–724.9)

Conclusion: Serum CTHRC1 is a promising biomarker for evaluation of RA patients. It can be used as a marker for RA diagnosis and in monitoring the disease activity and severity.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune progressive disease of synovial joints [1]. It is a multifactorial disease as genetic and non-genetic factors contribute in a complex disease pathology [2]. The diagnosis of RA is mainly based on clinical manifestations, radiological findings and laboratory investigations include inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR); autoantibodies, like rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP). However, CRP and ESR are non-specific laboratory indicators, which are affected by many factors as aging and can only reflect short-term inflammatory status [3]. RF is detected in 60–70% of RA patients [4] with limited specificity as it is often absent early in the disease course and can be found in other autoimmune and inflammatory diseases. CCP autoantibodies provide high specificity for RA with moderate sensitivity [5].

Early diagnosis of RA has an important matter in clinical practice, as it helps in effective control of disease activity, reduces the permanent disability which has essential rule in the long term outcome of the disease and its progression [6]. Many Egyptian studies on RA investigated the role of different biomarkers in determining clinical significance and monitoring the disease activity [7,8], some of them have been focused on the diagnostic potency [9,10].

Persistent synovitis leads to pannus formation, a new pathological tissue formation that invades and erodes adjoining cartilage and bone. Pannus is a main cause for pain, swelling, tissue destruction, joint deformities and bone erosion in RA patients [11]. Fibroblast-like synoviocytes (FLS), especially the invasive and migratory cadherin-11-positive subtype [12], are the main components of synovial pannus tissue and considered active drivers in RA pathogenesis [11].

Collagen triple helix repeat containing 1 (CTHRC1) protein is expressed in a number of embryonic and neonate tissues, including

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developing cartilage and bone [13]. CTHRC1 was found strongly associated with the murine proteoglycan-induced arthritis severity and collagen antibody-induced murine arthritis (CAIA)[14]. Moreover, CTHRC1 expression in murine experimental arthritis is increased in the synovium and revealed specifically in activated murine and human RA-FLS[14] located at the synovial intimal lining and at the bone-pannus interface [15].

The aim of this work was to assess serum collagen triple helix repeat containing 1 (CTHRC1) protein level in rheumatoid arthritis (RA) patients and compare it with healthy controls. In addition, to evaluate the relation of its level with RA activity and severity.

2. Patients and methods

This cross-sectional study was carried out at the Rheumatology and Rehabilitation Department, Faculty of Medicine, Assiut University. It included 60 RA patients aged ≥ 18 years diagnosed according to the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria [16]. Sixty age and gender matched healthy individuals were enrolled as a control group. Patients with malignancy or any other autoimmune disease were excluded. The study was approved by the ethics committee of the Faculty of Medicine, Assiut University, Egypt. Informed consent was obtained from all participants after explanation of the study aims and procedures.

The socio-demographic data, detailed medical history and thorough clinical examination were assessed for all patients. Therapeutic history and radiographic findings were recorded. Swollen joint count (SJC) and tender joint count (TJC) were estimated. The visual analogue scale (VAS) was reported by the patients and physician according to the patient global assessment (PGA) and physician global assessment (PhGA) of the disease activity respectively. RA activity was evaluated using disease activity score 28 (DAS28) [17] and categorized accordingly into remission < 2.6; low 2.6 to ≤ 3.2; moderate > 3.2 to ≤ 5.1; and high > 5.1. The modified health assessment questionnaire (MHAQ) [18] was used to evaluate functional status of the patients. Disease severity was assessed by RA medical records-based index of severity (RARBIS) [19]. Laboratory investigations included Complete blood picture (CBC), liver function tests: [serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT)], kidney function tests:[blood urea (BUN), serum creatinine], ESR, CRP, RF and anti-CCP antibodies were performed for RA patients.

Serum CTHRC1 levels were measured in patients and controls by collecting 5 ml venous blood into plain tubes after complete aseptic conditions, left to clot for 30 min at 37 °C and centrifuged at 3000 rpm. The separated serum was stored at −80 °C for subsequent determination of serum CTHRC1.Quantitative determination of CTHRC1concentration was done using Sino Gene Clon Biotech Co., Enzyme-Linked Immunosorbent Assay (ELISA) Kit, China. Catalog no. SG-12024

Statistical analysis: Data analysis was undertaken using SPSS version 20. Data were presented as frequencies and percentages or mean and standard deviation. After testing data normality, non-parametric tests were performed. Mann Whitney *U* test and Kruskal Wallis test were used for comparison. Spearman's correlation was considered. Receiver operating characteristic (ROC) curve analysis was done to identify diagnostic ability of CTHRC1 to predict disease among patients and controls. Multivariate linear regression analysis was used to identify factors predicting increase in CTHRC1 among RA patients. The p-value < 0.05 was considered significant.

3. Results

The study included 60 RA patients; 49 (81.7%) females and 11 (18.3%) males. Their age mean was 43.6 ± 10.8 (20–65) years and disease duration was 8.8 ± 0.9 (0.5–28) years. The controls were matched for gender: 50 (83.3%) females and 10 (16.7%) males and age (39.8 ± 12.6; 20–60 years) (p = 0.81, p = 0.06).The clinical manifestations and laboratory investigations of RA patients are presented in table 1.

Regarding the medications used; hydroxychloroquine (HCQ) was used by 59 (98.3%), methotrexate (MTX) by 47 (78.3%), leflunomide (LFN) by 40 (66.7%) of the study patients. While 5 patients (8.3%) were treated by sulfasalazine (SAZ) and anti-tumor necrosis factor-α (antiTNF-α) drugs were used by 3(2.1%). Steroids and non– steroidal anti-inflammatory drugs (NSAIDs) were used by 42/58 (70% and 96.7%) respectively. The mean SJC and TJC were 3.7 ± 0.9 (0–24), 12.3 ± 1.3 (0–28) respectively. The PGA and PhGA were 4.4 ± 0.3 (2–10) in both. The mean of DAS28 was 4.9 ± 2 (1.95–8.6). 9 patients were in remission; 12/9/30 had low/ moderate/ high disease activity respectively. The mean MHAQ was 0.9 ± 0.3 (0.13–1.5) while RARBIS was 9.3 ± 2.2 (4–13).

The mean of serum CTHRC1 level in RA patients (1009.5 ± 79. 4 ng/ml; 579.5–3715 ng/ml) was significantly higher than in controls 470.7 ± 8.2 ng/ml; 333.5–583.5 ng/ml)(p < 0.001) (Fig. 1). The diagnostic ability of CTHRC1 for differentiation between

Table 1
Clinical manifestations and laboratory investigations of rheumatoid arthritis patients.

	Parameter mean ± SD (range) or n (%)	RA patients (n = 60)
General	Morning stiffness	60 (100.0)
	Fatigue	47 (78.3)
	Fever	5 (8.3)
	Anorexia	11 (18.3)
	Weight loss	26 (43.3)
	Hypertension	7 (11.7)
Musculoskeletal	Arthralgia	60 (100.0)
	Arthritis	58 (96.7)
	Deformity	25 (41.7)
	Myalgia	42 (70.0)
	Limitation of movements	26 (43.3)
	Trigger finger	15 (25.0)
	Subcutaneous nodules	24 (40.0)
Eye	Dryness	11 (18.3)
	Red burning eyes	2 (3.33)
Cardio-pulmonary	Dyspnea	46 (76.7)
	Cough	23 (38.3)
	Chest pain	7 (11.7)
Renal	Dysuria	21 (35.0)
GIT	Abdominal colic	6 (10.0)
Laboratory investigations	Hemoglobin (g/dl)	12.19 ± 1.59 (8.9–16.1)
	WBCs ($x10^3$/ul)	6.54 ± 1.9 (3.3–13.1)
	Platelets ($x10^3$/ul)	328.75 ± 8.3 (182–512)
	ESR (mm/1st hr)	38.66 ± 3.99 (5–132)
	CRP (mg/l) (+ve in 54)	14.74 ± 3.03 (0.23–153.9)
	AST (U/L)	19.5 ± 1.22 (6.7–34)
	ALT (U/L)	20.98 ± 3.87 (6–45)
	Serum albumin (g/L)	42.6 ± 3.68 (30–49.26)
	Blood urea (mmol/L)	4.62 ± 0.54 (1.8–28)
	Serum creatinine (umol/l)	58.66 ± 1.87 (30–90)
	RF (IU/ml) (+ve in 44)	131.18 ± 22.3 (3.3–699)
	Anti CCP (U/ml) (+ve in 40)	79.3 ± 11.53 (0.5–200)

RA: rheumatoid arthritis, GIT: gastrointestinal, WBC: white blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, RF: rheumatoid factor, anti CCP abs: anti-cyclic citrullinated peptide antibodies

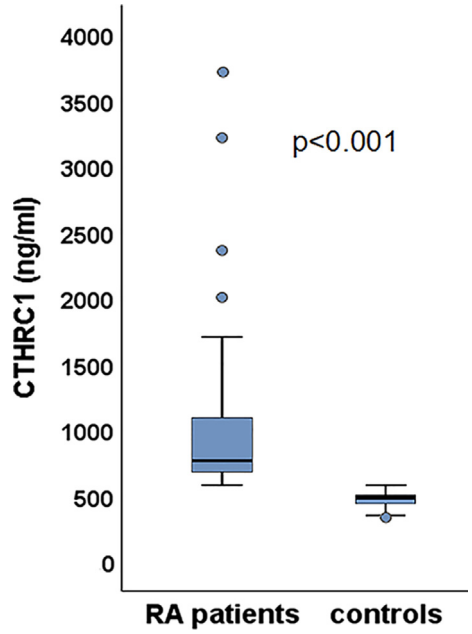

Fig. 1. Box plot for serum CTHRC1 levels in rheumatoid arthritis patients and controls.

patients and controls is illustrated by ROC curve analysis (Fig. 2) and showed that the optimum cut-off values above which CTHRC1 can predict disease was > 583.5 ng/ml with sensitivity of 98.3%, specificity of 100%, positive predictive value (PPV) of 100%, negative predictive value (NPV) of 98.4% and area under the curve (AUC) 0.99, 95% confidence interval (CI) was 0.998 – 1 (p < 0.001).

Serum CTHRC1significantly correlated with DAS28 (r = 0.81, p < 0.001), MHAQ (r = 0.41, p = 0.002) and RARBIS (r = 0.41, p = 0.006). No significant correlation was found with age or disease duration. Significant correlations were found between serum CTHRC1 with ESR (r = 0.57, p-<0.001), CRP (r = 0.41, p = 0.002), RF (r = 0.31, p = 0.037) and anti CCP antibodies (r = 0.27, p = 0.036).

The increase of disease activity was associated with an increase in serum CTHRC1 levels (Table 2). No significant differences can be detected in serum CTHRC1 levels between RA patients with positive RF and anti-CCP antibodies and those had negative results (p = 0.57, 0.53 respectively) .

Multivariate linear regression for the increase in serum CTHRC1 levels among patients revealed that the DAS28 (ß=287.6; p = 0.007, CI = 83.4–491.9) and MHAQ score (ß=369.7; p = 0.04, CI = 14.5–7 24.9) were significant predictors.

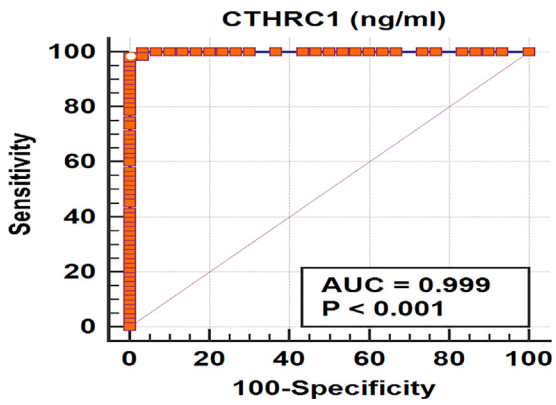

Fig. 2. Receiver operating characteristic (ROC) curve for prediction rheumatoid arthritis by serum CTHRC1 level.

Table 2
Association between CTHRC1 levels with disease activity level in rheumatoid arthritis patients.

Activity level mean ± SD (Range)		CTHRC1 ng/ml in RA patients (n = 60)	p-value
DAS28	Remission (n = 9)	614.9 ± 20.5 (579.5–636)	**<0.001**
	Low (n = 12)	675.3 ± 14.2 (648.5–691)	
	Moderate (n = 9)	732.4 ± 18.3 (702.5–758)	
	High (n = 30)	1344.7 ± 133.6 (767.5–3715)	

*Kruskal Wallis Test
Bold values are significant at p < 0.05

4. Discussion

Rheumatoid arthritis is chronic progressive autoimmune disease that involves mainly the joint synovial tissue and is accompanied by pannus hyperplasia and progressive bone destruction, which leads ultimately to joint function loss [20]. Although several genetic and environmental factors have been associated with an increased RA risk, the eventual pathogenesis remains obscure [21]. RA has significant variation in clinical presentation, the presence of specific serological markers and the extent of joint and bone degradation [22]. Diversity of the disease manifestations, atypical early presentation and negative serology can lead to misdiagnosis and delay the best time for treatment [23]. It is still of important clinical significance to search for new indicators useful in RA diagnosis and monitoring.

CTHRC1 is a secreted modulator of Wnt signaling, which is a main joint remodeling regulator [24] and promotes cell proliferation and migration [15]. CTHRC1 expression pattern in pannus, its role in FLS function relevant to cartilage damage in RA and its association with disease severity in murine arthritis highlighted its role as a marker for RA diagnosis and disease activity monitoring [25]. Recent studies [20,25] with relatively hopeful results investigated the role of CTRHC1 in RA diagnosis.

In this study, the mean of serum CTHRC1 levels in patients was significantly higher than in controls. This is consistent with findings of other studies [15,20,25]. In this work, the diagnostic ability of CTHRC1 for differentiation between RA patients and controls can significantly predict disease at a cut off value of > 583.5 ng/ml with sensitivity of 98.3%, specificity of 100%, AUC 0.99.The present study finding was superior to *Myngby et al* [25] and *Hu and co-workers* [20] who reported availability of CTRHC1 to differentiate RA and controls with sensitivity of 62%, 84.5% and a specificity of 86%, 75.6% respectively.

CTHRC1 protein overexpression in smooth muscle cells and embryonic fibroblasts is associated with increased cell migration properties [26]. The endogenous CTHRC1 expression has been found in many types of metastatic solid cancer and the inhibition of its expression results in decreased cell migration in vitro [27]. Immuno-histochemical analysis of many human primary cancers and metastases has revealed limitation of CTHRC1 expression to the stromal cells of solid tumors [28,29]. Furthermore being a recognized marker of enhanced cancer metastases, CTHRC1 is overexpressed in inflammatory conditions of murine arthritis [15]. The CTHRC1 gene was strongly associated with the murine collagen antibody-induced arthritis (CAIA) severity,CTHRC1 mRNA is highly inducible in CAIA synovial joints inflammation and CTHRC1 protein content increases > 10 folds within 3 days from a undetectable basic level [14].Interestingly, whileCTHRC1 is strongly expressed in patients with solid tumors, plasma CTHRC1 did not elevate in those patients [29–31].This discrepancy indicates that CTHRC1 regulation in the circulation might depend on tissue vascularization, protein stability and different sites of protein production. Being as arthritis inducible, specific for the arthritic pannus

and able to be secreted into circulation, CTHRC1 could be a promising marker for RA [15].

A potential role of CTRHC1 in RA has been determined as its levels significantly correlated with disease activity score (DAS28). Moreover, the higher level of the disease activity of RA patients, the higher levels of CTHRC1 indicating the possible benefit of using serum CTHRC1 levels in monitoring RA disease activity.

This study also revealed a significant correlation between serum CTHRC1 levels and ESR, CRP, RF as well as anti CCP abs. These findings were compatible with *Shekhani and co-workers* [15] results that demonstrated higher human CTRHC1 plasma levels associated with increased CRP and DAS28. *Myngby and colleagues* [25] showed that CTHRC1 levels in RA patients were significantly elevated when compared to patients with osteoarthritis and reactive arthritis as well as healthy controls. It also revealed a significant relation of CTRHC1 with SJC, CRP, RF, ACPA and disease activity.

In this study, significant correlations were present between serum CTRHC1 serum and RA severity assessed by RARBIS score as well as functional status of RA patients evaluated by MHAQ score. To the best of our knowledge, no other studies assessed such relations.

This study is limited by a relatively small sample size and its cross-sectional design make it is difficult to evaluate the association between CTHRC1 and RA disease progression. Further longitudinal studies with larger sample size may be needed to assess the predictive potential of serum CTHRC1 in RA.

In conclusion, serum CTHRC1 is a promising biomarker for evaluation of RA patients. It can be used in RA diagnosis with high sensitivity and specificity. Remarkable relations found in serum CTHRC1 levels with disease activity and severity makes it a possible valuable marker for monitoring RA patients.

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CRediT authorship contribution statement

Zahraa I. Selim: Conceptualization, Methodology, Supervision, Writing - review & editing. **Rania M. Gamal:** Conceptualization, Methodology, Supervision, Writing - original draft. **Lobna A Araby:** Conceptualization, Methodology, Data curation, Software. **Eman R. Badawy:** Conceptualization, Methodology, Investigation. **Nada M. Gamal:** Conceptualization, Methodology, Writing - original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Testa D, Calvacchi S, Petrelli F, Giannini D, Bilia S, Alunno A, et al. One year in review 2021: pathogenesis of rheumatoid arthritis. Clin Exp Rheumatol. 2021;39(3):445–52.
[2] Eyre S, Bowes J, Diogo D, Lee A, Barton A, Martin P, et al. High-density geneticmapping identifies new susceptibility loci for rheumatoid arthritis. Nat Genet. 2012;44(12):1336–40.
[3] He Y, Tang J, Wu B, Yang B, Ou Q, Lin J. Correlation between albumin to fibrinogen ratio, C-reactive protein toalbumin ratio and Th17 cells in patients with rheumatoid arthritis. Clin Chim Acta 2020;500:149–54.
[4] Nell VP, Machold KP, Stamm TA, Eberl G, Heinzl H, Uffmann M, et al. Autoantibody profiling as early diagnostic and prognostic tool for rheumatoidarthritis. Ann Rheum Dis. 2005;64:1731–6.
[5] Song YW, Kang EH. Autoantibodies in rheumatoid arthritis: rheumatoid factors and anti-citrullinated protein antibodies. QJM 2010;103(3):139–46.
[6] Trouw LA, Huizinga TW, Toes RE. Autoimmunity in rheumatoid arthritis: different antigens-common principles. Ann Rheum Dis 2013;72:ii132-6.
[7] Allam SI, Sallam RA, Elghannam DM, El-Ghaweet AI. Clinical significance of serum B cell chemokine (CXCL13) in early rheumatoid arthritis patients. Egyptian Rheumatologist 2019;41(1):11–4.
[8] Hussein N, Kamel N, Fouda N, Farrag D. Peptidyl-arginine deiminase-type IV as a diagnostic and prognostic marker in rheumatoid arthritis patients.Egyptian. Rheumatologist. 2019;41(2):87–91.
[9] Hameed AKM, El-Said TO, Askar HY, ElKady BA. Performance of serum adenosine deaminase in measuring disease activity in rheumatoid arthritis patients. Egyptian Rheumatologist. 2019;41(2):81–5.
[10] Mohamed SR, Neseem NO, Metwally SS, El-Kady BA. Diagnostic value and clinical significance of anti-carbamylated protein (anti-CarP) antibodies in Egyptian patients with rheumatoid arthritis. Egyptian Rheumatologist. 2020;42(1):1–4.
[11] Bartok B, Firestein GS. Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis. Immunol Rev. 2010;233:233–55.
[12] Kiener HP, Niederreiter B, Lee DM, Jimenez-Boj E, Smolen JS, Brenner MB. Cadherin 11 promotes invasive behavior of fibroblast-like synoviocytes. Arthritis Rheum. 2009;60(5):1305–10.
[13] Durmus T, LeClair RJ, Park K-S, Terzic A, Yoon JK, Lindner V. Expressionanalysis of the novel gene collagen triple helix repeat containing-1 (Cthrc1). Gene Expr Patterns. 2006;6(8):935–40.
[14] Kudryavtseva E, Forde TS, Pucker AD, Adarichev VA. Wnt signaling genes of murine chromosome 15 are involved in sex-affected pathways of inflammatory arthritis. Arthritis Rheum. 2012;64(4):1057–68.
[15] Shekhani MT, Forde TS, Adilbayeva A, Ramez M, Myngbay A, Bexeitov Y, et al. Collagen triple helix repeat containing 1 is a new promigratory marker of arthritic pannus. Arthritis Res Ther. 2016;18(1). doi: https://doi.org/10.1186/s13075-016-1067-1.
[16] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580–8.
[17] Prevoo MLL, Van'T Hof MA, Kuper HH, Van Leeuwen MA, Van De Putte LBA, Van Riel PLCM. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38(1):44–8.
[18] Pincus T, Summey JA, Soraci SA, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis Rheum 1983;26(11):1346–53.
[19] Cabral D, Katz JN, Weinblatt ME, Ting G, Avorn J, Solomon DH. Development and assessment of indicators of rheumatoid arthritis severity: results of a Delphi panel. Arthritis Rheum 2005;53(1):61–6.
[20] Hu T, Liu Y, Tan L, Huang J, Yu J, Wu Y, et al. Value of serum collagen triple helix repeat containing-1(CTHRC1) and 14-3-3η protein compared to anti-CCP antibodies and anti-MCV antibodies in the diagnosis of rheumatoid arthritis. Br J of Biomed Sci 2021;78(2):67–71.
[21] Feldmann M. Development of anti-TNF therapy for rheumatoid arthritis. Nat Rev Immunol 2002;2(5):364–71.
[22] Lindstrom TM, Robinson WH. Biomarkers for rheumatoid arthritis: making it personal. Scand J Clin Lab Invest Suppl. 2010;242:79–84.
[23] Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. J. The Lancet 2016;388(10055):2023–38.
[24] Baron R, Rawadi G. Targeting the Wnt/beta-catenin pathway to regulate bone formation in the adult skeleton. Endocrinology 2007;148:2635–43.
[25] Myngbay A, Bexeitov Y, Adilbayeva A, Assylbekov Z, Yevstratenko BP, Aitzhanova RM, et al. CTHRC1: A New Candidate Biomarker for Improved Rheumatoid Arthritis Diagnosis. Front Immunol 2019;10. doi: https://doi.org/10.3389/fimmu.2019.0135310.3389/fimmu.2019.01353.s00110.3389/fimmu.2019.01353.s002.
[26] Pyagay P, Heroult M, Wang Q, Lehnert W, Belden J, Liaw L, et al. Collagentriple helix repeat containing 1, a novel secreted protein in injured and diseased arteries, inhibits collagen expression and promotes cell migration. Circ Res. 2005;96(2):261–8.
[27] Tang L, Dai DL, Su M, Martinka M, Li G, Zhou Y. Aberrant expression ofcollagen triple helix repeat containing 1 in human solid cancers. Clin Cancer Res. 2006;12(12):3716–22.
[28] Kharaishvili G, Cizkova M, Bouchalova K, Mgebrishvili G, Kolar Z, Bouchal J. Collagen Triple Helix Repeat Containing 1 Protein, periostin and versican in primary and metastatic breast cancer:an immunohistochemical study. J Clin Pathol. 2011;64(11):977–82.
[29] Duarte CW, Stohn JP, Wang Q, Emery IF, Prueser A, Lindner V, et al. Elevated plasma levels of the pituitary hormone cthrc1 in individuals with red hair but not in patients with solid tumors. PLoS ONE 2014;9(6):e100449.
[30] Huang C-F, Lira C, Chu K, Bilen MA, Lee Y-C, Ye X, et al. Cadherin-11 increases migration and invasion of prostate cancer cells and enhances their interaction with osteoblasts. Cancer Res. 2010;70(11):4580–9.
[31] Kaur H, Phillips-Mason PJ, Burden-Gulley SM, Kerstetter-Fogle AE, Basilion JP, Sloan AE, et al. Cadherin-11, a Marker of the Mesenchymal Phenotype, Regulates Glioblastoma Cell Migration and Survival In Vivo. Mol Cancer Res. 2012;10(3):293–304.