Role of serum Collagen triple helix repeat containing 1(CTHRC1) protein in autoimmune diseases

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Abstract

Background: Background: Collagen triple helix repeat containing-1 (CTHRC1), is a 28-kD extracellular matrix glycoprotein**.** CTHRC1 is expressed mostly in adventitial fibroblasts and increases cell motility by limiting the deposition of collagen matrix and promoting cell migration**.** CTHRC1 is produced by activated fibroblast-like synoviocytes (FLS) and primarily promoted FLS polarization and increased the migration speed and directness of cell movement which resulted in production of arthritic pannus**.** RA has great variation in clinical presentation, the presence of specific serological markers and the extent of joint involvement and bone erosion**.** SLE is heterogeneous in presentation characterized by many pathogenic autoantibodies and uncontrolled inflammatory response leading to organ damage.So it is of importance to search for markers for better evaluation and monitoring of both diseases

Introduction

Rheumatoid arthritis is a chronic and progressive autoimmune disease which mainly involves the synovial tissue of the joints and is accompanied by hyperplasia of pannus and progressive bone destruction which eventually leads to loss of joint function. (**1**)

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). But CRP and ESR are non-specific laboratory indicators, and can only reflect short-term inflammatory status **(2**).

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by B cell dysfunction, production of autoantibodies directed toward cellular and nuclear components, and multiorgan damage caused by immune complex deposition and inflammation within affected tissues **(3)**

SLE is heterogeneous in presentation, with a broad spectrum of clinical manifestations ranging from clinically mild self-resolving symptoms to severe life-threatening organ involvement and may be limited to the single organ or can cause a widespread systemic involvement **(4)**

There is still lack of diagnostic and prognostic biomarkers for better patient evaluation. Several tests have emerged as CTHRC1 protein .(**5**)

Epidemiology: RA is one of the most prevalent chronic inflammatory diseases .With a prevalence ranging from 0.4% to 1.3% of the population depending on both sex (women are affected two to three times more often than men), age (frequency of new RA diagnoses peaks in the sixth decade of life), and studied patient collective (RA frequency increases from south to north and is higher in urban than rural areas).(**6**)

The prevalence of SLE varies depending on geographical location, race, age and gender . In the United States, the prevalence rates vary from 20 and 150 cases per 100,0000 , outnumbering the prevalence rates found in African populations the prevalence is higher among African Americans (406 cases per 100,000) compared with Caucasians (164 cases per 100,000) **(7)**. The overall estimated prevalence of adult SLE patients in Egypt was 6.1/100,000 population (1.2/100,000 males and 11.3/100,000 females).(**8**)

Clinical manifestations:

RA is typically a distal, symmetrical, small joint polyarthritis, most commonly involving the (MCP) and (PIPs), interphalangeal joints of the thumbs, the wrists, and (MTP). Other joints of the upper and lower limbs, such as the elbows, shoulders, ankles and knees are also commonly affected (**9**) .

The extra-articular manifestations of RA can occur at any age after onset and more frequently seen in patients with severe, active disease and those who have RF and/or are HLA-DR4 positive including the skin, eye, heart, lung, renal, nervous and gastrointestinal systems. Clinical manifestations such as vasculitis, visceral nodules, Sjögren's syndrome, or pulmonary fibrosis present.Subcutaneous Nodules are the most common extra-articular feature, and are present in up to 30%.(**10**)

Systemic lupus erythematosus is a complex autoimmune disease with a chronic relapsing–remitting course and wide spectrum manifestations ranging from mild to severe illness (**11**) .

The most prominent feature in SLE is an immune response to nucleic acid and associated proteins, which leads to the production of massive autoantibodies, the formation of immune complex, and damage to various organs including the skin, joints, liver, kidneys, heart, lungs, blood vessels and brain.(**12**)

Structure of CTHRC1 protein:

CTHRC1 is a secreted 28 kDa glycoprotein . The human protein contains N-terminal hydrophobic signal peptide of 30 amino acids in length that directs CTHRC1 for secretion, a short collagen triple helix repeat (CTHR) domain consisting of 12 repeats of the Gly-X-Y motif, and a highly conserved C-terminal domain with structural homology to the globular C1q domain of collagens VIII and X domain . The CTHR domain may promote CTHRC1 dimer or trimer formation and mediate interaction with a variety of ligands.(**13)**

The domain structure of CTHRC1 is similar to that of adiponectin, which belongs to the C1q/tumor necrosis factor (TNF)-related protein superfamily. Thus,secreted CTHRC1 may share structural characteristics with this protein superfamily. CTHRC1 is also a cysteine-rich protein: 10 conserved cysteine residues are distributed between residues 55 to 243 (9 of which are located within the C1q domain;. The single putative N-glycosylation site at amino acid 186 has been reported to stabilize the protein and may promote the tethering of secreted CTHRC1 to the plasma membrane**.** (**5**)

Activity of CTHRC1 occurs following the cleavage at glutamic acid residue 46(E46) and arginine residue 96 (R96) by plasmin, as it does not have a pro-peptide cleavage site. **(14)**

Functions of CTHRC1 protein:

Collagen triple helix repeat containing 1 (CTHRC1) inhibits glycogen matrix deposition and promotes cell migration. **(14)**

CTHRC1 was not detectable in normal arteries, indicating that the protein plays a specific role in the wound-healing response and promotes vascular remodeling during arterial injury .CTHRC1 expression has been correlated with conditions and processes associated with deregulated wound and tissue repair, including liver and lung fibrosis and myocardial infarction, liver injury caused by Hepatitis B infection (**5**)

The expression of CTHRC1 is related to tumor angioigenesis, proliferation, invasion, and metastasis in various human malignancies, including gastric cancer, pancreatic cancer, hepatocellular carcinoma, keloid, breast cancer**.(15)**

CTHRC1 is secreted by osteoclasts. It targets stromal cells to stimulate osteogenesis, enhances the differentiation and function of osteoblast, and upregulates osteoblastic bone formation,which suggests its important role in bone formation and bone mass maintenance (**16**)

Expression of CTHRC1 protein:

CTHRC1 is transiently expressed by fibroblasts in remodeling adventitia and by smooth muscle cells in the neointima of injured tissue. In injured arteries and skin, the expression of CTHRC1 is associated with myofibroblasts and locates in the sites of collagen matrix deposition. In adults, CTHRC1 is expressed only in bone matrix and periosteum. CTHRC1 is also found in the matrix of calcifying atherosclerotic plaques and mineralized bone of skeletal tissues in humans .In other tissues, the sites of CTHRC1 expression overlap considerably with interstitial collagens and transforming growth factor-β (TGF-β) family members, particularly bone morphogenetic proteins (BMPs). The sites of CTHRC1 expression are characterized by the presence of active TGF-β and abundant collagen synthesis. **.(15)**

Collagen triple helix repeat containing 1 (CTHRC1) protein is expressed in a number of embryonic and neonate tissues, including developing cartilage and bone. (**17**)

CTHRC1 appears to be expressed mainly in tissues which undergo remodeling including myocardium, the renal arteries, injured skin, differentiated smooth muscle, as well as in osteoblasts, osteoclasts and osteocytes. **(18).**

CTHRC1 protein and RA:

The pathogenesis of RA is attributed to a complex interaction between genetic and environmental factors and the repeated activation of innate and adaptative immune system evolves into the breakdown of immune tolerance, aberrant autoantigen presentation and antigen-specific T and B cells activation. All these events culminate in synovial hyperplasia and bone destruction leading to joint swelling and deformity and to systemic inflammation**.(19)**
Synovial hyperplasia is a hallmark of RA pathogenesis and characterized by the formation of pannus. Rheumatoid synoviocyte which consist of fibroblast like synoviocyte and synovial macrophage form the leading edge of pannus .fibroblast-like synoviocytes (FLS) in the synovial intimal lining are key drivers of bone erosion in RA; these cells become hyperproliferative and acquire an aggressive migratory and invasive phenotype. These cells are also a source of numerous pro-inflammatory cytokines, growth factors and cartilage- and bone-degrading proteases, co-operate with macrophage- like progenitor cells, leading to local formation of osteoclasts, which invade the subchondral bone using acid attack and acidic proteinases. RA-FLSs contributes to the inflammatory microenvironment and promotes pannus invasion.(**5)**
CTHRC1 is produced by activated fibroblast-like synoviocytes (FLS) remarkably located at the synovial intimal lining and the bone-pannus interface and it is also highly expressed in plasma from rheumatoid arthritis patients. CTHRC1 primarily promoted FLS polarization along the front-tail axis and increased the migration speed and directness of cell movement, and then resulted in the abundant production of arthritic pannus and consequent damage of arthritis. CTHRC1 protein promotes bone and cartilage erosion and pannus formation by activating fibroblast-like synoviocytes (FLS). (**20**).
There is significant association of CTHRC1 with inflammatory cytokines such as IL-1β, IL-6, IL-8, and IFNγ which have major role in RA pathogenesis. **(14)**
Wnt signaling pathway is considered to be one of the major mechanisms of RA pathogenesis. Wnt signaling plays crucial roles in cell proliferation, differentiation, migration, cell adhesion and embryonic development . studies showed upregulated expression of β- catenin in Rheumatoid Arthritis (RA) fibroblast-like synoviocytes (RA-FLS), caused by the canonical Wnt signaling pathway. **(14)**
CTHRC1 protein can participate in the remodeling of RA synovial tissue by activating the classic Wnt signal pathway. **(1).**

CTHRC1 protein and SLE:

systemic lupus erythematosus (SLE), is characterized by various activation both of T and B lymphocytes, production of large quantities of autoantibodies, and formation of immune complexes that result in tissue and organ damage. (**21,22**).
There is a complex interaction between gene susceptibility, hormonal influences and environmental triggers, with a breakdown of immune tolerance. This results in dysregulation of the inflammatory response (**23**)

During vascular development and upon injury, TGF-β mediates several negative regulatory effects during vessel repair by upregulating collagen synthesis via activation of SMAD2/3 complexes, leading to increased collagen deposition and smooth muscle cell proliferation. (**24**)
Activation of the TGF-β signaling pathway also induces expression of CTHRC1. CTHRC1 inhibits TGF-b signaling by accelerating degradation of phospho-Smad3 through a proteosomal pathway.(**25**)
Transforming growth factor beta 1 (TGF-b1) belongs to a large family of multifunctional proteins, and it exerts broad anti-inflammatory and immunosuppressive effects and plays an important role in self-tolerance.(**12)**
In SLE, the destructive inflammation leads to the damage of blood vessels and production of CTHRC1, then the latter depresses TGF-b signaling, which results in the occurrence and development of autoimmunity as a result of weakened immunosuppressive effects in patients with SLE **.(12)**

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