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DIAGNOSTIC VALUE OF ADAMTS-7 IN JOINT DISEASES

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Abstract
Reactive arthritis (ReA) is a "sterile" inflammatory joint disease in which infectious agents and their antigens are absent in the synovial fluid and synovial membrane of patients. ReA is a seronegative spondyloarthritis, which meets the criteria of the European Group for the Study of Spondyloarthritis. With the introduction into clinical practice in the early 90s of the reverse transcriptase polymerase chain reaction (RT–PCR) method, small amounts of Ch.trachomatis DNA and RNA were found in the joint cavity. The presence of these nucleic acids, which have a very short lifetime in tissues (several minutes), indicated the possibility of transcription and, consequently, active reproduction of bacteria in the joint cavity.

Keywords: ADAMTS-7, reactive arthritis, joints syndrome.

Introduction

ADAMTS is a group of disintegrin and metalloproteinases with thrombospondin multidomain protease enzymes. ADAMTS-7 is a member of the ADAMTS family and plays an important role in the pathogenesis of arthritis. Overexpression of the ADAMTS-7 gene promotes degradation of the complex oligomeric matrix protein (COMP) and accelerates the development of arthritis. Furthermore, ADAMTS-7 and tumor necrosis factor-α (TNF-α) form a positive feedback loop in arthritis. Most importantly, granulin-epithelin precursor, a growth factor, plays an important role in bone development and bone-related diseases, disrupting the interaction between ADAMTS-7 and COMP and preventing COMP degradation. This review highlights the ADAMTS-7 protein, including its structure, function, gene regulation, and involvement in inflammatory diseases.

The ADAMTS (A disintegrin and metalloproteinase with thrombospondin Motifs) proteinase family consists of 19 members of this family. It consists of multi-domain proteolytic enzymes and plays important roles in a number of pathophysiological processes, including COMP assembly and degradation, hemostasis, angiogenesis, organogenesis, and cancer and arthritis. [1]. The ADAMTS gene was first cloned as an inflammation-related gene in mice [2]. In general, the structure of ADAMTS proteins

includes a prodomain, metalloproteinase, disintegrin-like, and thrombospondin repeats [3]. Human ADAMTS proteins can be divided into four subgroups based on sequence alignment and functional differences [4]. The first subgroup includes ADAMTS-1, -4, -5, -8, -9, -15, and -20 and degrades aggrecan, a major proteoglycan core protein found only in the spine. A second subgroup consisting of ADAMTS-2, -3 and -14 cleaves peptides of procollagen [5-8]. Only ADAMTS-13 constitutes the third subgroup and is essential for von-Willebrand factor (vWF) [9]. ADAMTS-7 and -12, which specifically bind to and cleave the oligomeric matrix protein (COMR), belong to the fourth subgroup [10-13].

Thus, ADAMTS-7 is a proteolytic member of the ADAMTS family, which contains a signal peptide, a prodomain, a metalloproteinase domain, a disintegrin-like domain, and multiple thrombospondin type I (TPS1) repeats. [14, 15]. The prodomain is generally thought to be important for maintaining enzyme latency. Cleavage of the ADAMTS propeptide by furin or furin-like enzymes is usually required for enzyme activity. For example, furin is the main convertase required for the production of ADAMTS-7 [13]. Macroglobulin α2 binds to ADAMTS-7 and forms a new substrate of ADAMTS-7 [10], and only the metalloproteinase domain of ADAMTS-7 is required for the degradation of macroglobulin α2 [15]. Also, the catalytic domain is responsible for the degradation of COMP [14]. The disintegrin domain has sequence similarity to soluble snake venom disintegrins and acts as an important binding agent for substrates [17]. The C-terminal repeat between the disintegrin domain and the cysteine-rich domain of ADAMTS proteins is variable, with four and fourteen C-terminal repeats in ADAMTS-7 and ADAMTS-20, respectively [14 , 19]. The four C-terminal repeats of ADAMTS-7 are necessary and sufficient for interaction with COMP [10 , 12 , 20]. The spacer domain is the least frequent domain, co-occurring with the mucin domain between the third and fourth C-terminal repeats[13]. In contrast to other ADAMTS proteins, the function of the spacer domain is not important for interaction with ADAMTS-7 substrates, but for participation in the localization of the enzyme [15].

ADAMTS-7 is expressed in bone, cartilage, synovium, tendon, and ligament, all of which contain COMP [12, 14]. ADAMTS-7 has also been detected in meniscus, skeletal muscle, and adipose tissue [12, 14].

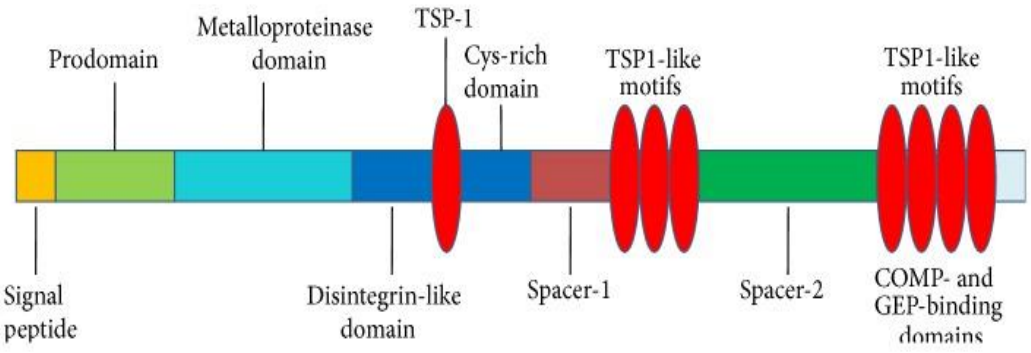

Figure 1. Domain structure and organization of ADAMTS-7.

ADAMTS-7 regulates tumor necrosis factor-α and interleukin-1β RNA in human tumor explants [10]. In addition, ADAMTS-7 elevation is associated with increased levels of tumor necrosis factor-α in patients with reactive arthritis [12] and hip fracture and various stages of hip osteoarthritis.[22].

In all tissues, cells are surrounded by an extracellular matrix. The extracellular matrix plays an important role in regulating cell shape, function, and behavior, and in cell differentiation, proliferation, and cell death [17]. The development of arthritic diseases is characterized by the breakdown and subsequent loss of the components of the extracellular matrix in the joint bone and cartilage. COMP is a multidomain glycoprotein composed of five subunits. COMP accounts for approximately 1% of tendon tissue weight and is the prominent non-collagenous component of tendon [26]. The development of pseudochondroplasia and epiphyseal dysplasia is associated with mutations in the human COMP gene, and they are mainly hereditary chondrodysplasias characterized by short stature and early-onset osteoarthritis [27–30]. The pathophysiological function of COMP may be to stabilize the articular cartilage extracellular matrix with matrix components such as collagen, aggrecan, and fibronectin. Degradative fragments of COMP have been detected in synovial fluid and serum of patients with traumatic ankle, knee injuries, primary osteoarthritis (OA) and rheumatoid arthritis (RA) [35, 36]. Thus, the isolation of COMP degradative enzymes is of great importance from the pathophysiological mechanism and therapeutic point of view [14].

Several matrix metalloproteinases can cleave purified COMP in vitro. These include MMP-1, MMP-3, MMP-9, MMP-13, MMP-19, and MMP-20 [37 , 38]. In addition, ADAMTS-7 proteinase can also cleave COMP protein in vitro [39]. The in vitro interaction between ADAMTS-7 and COMP was investigated in the presence of glutathione S-transferase, and the specific association between ADAMTS-7 and COMP was confirmed by an in vivo co-immunoprecipitation assay. Colocalized with ADAMTS-7 and COMP both in the cytoplasm and on the surface of human chondrocytes.

ADAMTS-7 recombinant enzyme purified in conditioned medium is able to cleave the COMP in vitro. The ADAMTS-7 domain produced as a glutathione S-transferase fusion protein in transgenic bacteria can also digest COMP in a time-dependent manner [12]. Surprisingly, the catalytic domain itself can break up COMP and generate three fragments, suggesting that ADAMTS-7 may digest COMP at multiple sites [12]. In addition, ADAMTS-7 is involved in the digestion of COMP protein by inflammatory cytokines TNF-α and IL-1β, and anti-ADAMTS-7 antibody effectively inhibits the production of COMP fragments [10].

No clear differences in ADAMTS-7 gene expression were observed between tissues of healthy and OA patients [14]. However, ADAMTS-7 mRNA was found to be significantly increased in tendon and synovium tissues of ReA patients. Increased COMP fragments were observed in the cerebrospinal fluid, synovial fluid, and serum of patients with OA and ReA [10]. These findings suggested that COMP degradation observed in OA and ReA patients may be associated with upregulation of ADAMTS-7.

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