Autoantibodies to type II collagen in rheumatoid arthritis and juvenile idiopathic arthritis: Meaning and clinical interest

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Type II collagen (CII) is the predominant collagen type in joint cartilage, constituting more than 50% of its dry weight [1]. Native CII consists of a triple-helix composed by three identical α chains. The collagen fibrils resist stretching forces caused by hydrophilic proteoglycan molecules in the extracellular matrix of articular cartilage, contributing to cartilage integrity [2]. The degradation of CII is associated with cartilage degeneration and loss of function in RA patients [3]. When CII is denatured the α chains are separated, and the antigenic sites (epitopes) present in the molecule are lost after disruption of the three dimensional structure [4]. Autoantibodies to native and denatured CII have been reported in rheumatoid arthritis (RA) [5-8] and juvenile idiopathic arthritis (JIA) [9-11], two autoimmune systemic inflammatory disorders. The levels of anti-CII antibodies detected may vary in the same patient at different times and also between patients, suggesting that these antibodies might be associated with specific events during arthritis development or even genetic susceptibility.

In mice susceptible to experimental collagen-induced arthritis (CIA), an autoimmune polyarthritis that shares several pathological features with RA can be induced by immunization with CII. This experimental model is the most commonly studied autoimmune model of RA [12, 13]. In the collagen antibody-induced arthritis (CAIA) model, immunization with anti-CII antibodies, directed towards several epitopes on CII in joint cartilage can induce polyarthritis that shares several pathological features with RA. This review focuses on the inflammatory events that may be associated with anti-CII production and also the clinical application of these antibodies in RA and JIA.

Keywords: Type II collagen; autoantibodies; rheumatoid arthritis; juvenile idiopathic arthritis

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CII degradation and cartilage damage
Articular cartilage damage is one of the key features of RA, ultimately leading to a loss of joint function [2]. In healthy joints, a thin layer of proteinaceous material covers the cartilage surface [15] inhibiting anti-CII antibodies binding [16]. In inflamed joints, CII epitopes are exposed to antibodies due to disruption of this proteinaceous layer. High levels of anti-CII antibodies might degrade CII molecules and induce an acute inflammation mediated by surface-bound immune complexes (ICs) containing antibodies against CII [7], which leads to the complement system activation and stimulate the production of proinflammatory cytokines such as tumor necrosis factor α (TNFα), interleukin-1β (IL-1β) and IL-8 [17], contributing for perpetuation of joint inflammation and consequently, cartilage damage. Antibodies to major CII epitopes are present at the inflammation site in RA patients, and have been detected in serum and synovial fluid samples from these patients, supporting the notion of a local increased immune response to CII in the joints [18]. Thus, although the involvement of anti-CII antibodies in the RA pathogenesis is still an open question, they could be useful as markers for the biomonitoring of joint destruction in some patients.

CII structure

The COL2A1 gene encodes an important component of the CII molecule, called pro-alpha1(II) chain [19]. The sequence of CII chains is conserved between different species, sharing many epitope sites and conserved domains (Figure 1). In CIA model, polyarthritis can be induced by immunization with CII from different species [20-24], indicating that arthritogenic epitopes are highly conserved. Furthermore, antibodies from RA patients can react to various heterologous CII molecules, such as mice, chicken, bovine, porcine and monkey [5, 18, 25]. Analysis of the CII triple-helix showed that numerous epitopes could be target by autoantibodies and responses against different CII epitopes may vary at different stages of the disease [26], which could help to explain the difference in the levels of anti-CII antibodies detected in different studies.

Clinical interest of anti-CII antibodies detection in RA and JIA patients

Many studies have evaluated the diagnostic performance of anti-CII antibodies detection in cohorts composed by RA
and JIA patients. The detection of these autoantibodies varies depending on the methodology employed and the CII type used as the antigen. Increased levels of anti-CII have been found in RA [27-29] and JIA patients during the early phase of the disease. DBA/1J CIA mice immunized with CII bovine also presented high titles of anti-CII antibodies immediately after the presentation of polyarthritis signs [31]. These findings support a major role of autoantibodies against CII in the pathophysiology of RA. It has been reported that in RA patients, high levels of autoantibodies specific for native human CII detected in the time of RA diagnosis were associated with early but not later signs of inflammation. This event could be explained by proinflammatory cytokine induction driven by surface-bound ICs containing anti-CII in early inflammatory processes [7]. High levels of anti-CII antibodies were also associated with an elevated degree of joint destruction at the time of diagnosis in RA patients [32]. On the other hand, anti-CII antibodies detected early in the disease course of JIA predicted joint damage when assessed eight years after disease diagnosis [30]. In a study about prevalence and avidity of anti-CII, autoantibodies displaying high avidity to CII were associated with disease activity in JIA patients [9]. The authors hypothesize that this event might be associated with treatment-resistant patients where the ICs production is not being blocked properly, resulting in active disease. They suggest that, a target therapy based on this mechanism could be highly promising for the treatment of RA and JIA patients with poor remission rate.

The prevalence of anti-CII has been reported between 8.8% and 88% in RA [5, 7, 33-36] patients and between 3.1% and 47% in JIA [9-11, 30] patients. In an investigation about the relationship between HLA-DR4/1 subtypes and T cell responses to CII antibodies in RA patients was observed that the HLA-DR4/1 positive group presented much higher positivity to CII antibodies (66.7%) than HLA-DR4/1 negative group (34.8%) [37], suggesting that genetic susceptibility may be associated with high levels of anti-CII antibodies detection. Table 1 provides a summary of autoantibodies detected against native and denatured CII in different studies involving RA and JIA patients. Due to the high differences in the levels of anti-CII reported in several studies and due to the lack of disease specificity, anti-CII antibodies are not considered as useful diagnostic biomarkers. In this context, studies focusing on the standardization of assays for anti-CII antibodies detection could be of great clinical interest.

In conclusion, it’s still not clear what the presence of anti-CII antibodies in RA and JIA patients’ means, and their use as biomarker to aid in diagnosis is still very controversial. From CIA mice studies we can deduce that type II collagen presents arthritogenic epitopes, which are capable of inducing an acute inflammation response very similar to that observed in RA patients. Anti-CII appearing around the early phase of the disease indicates that these autoantibodies may play a pivotal role in the immunopathogenesis of RA and JIA.

Conflict of interest

The authors declare no conflict of interest.

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