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Autoimmunity to Sa Peptide in Aggressive and Destructive Rheumatoid Arthritis

[Agresif ve yıkıcı romatoid artiritte Sa peptide karşı otoimmünite]

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ABSTRACT

Currently available data suggest that a spectrum of auto-antibodies is now known to be specifically associated with rheumatoid arthritis (RA). The RA specificity of the research based anti-Sa ELISA has been shown to be better than that of anti-CCP and RF while its sensitivity is less. Anti-Sa antibodies are highly specific for RA and are predominantly IgG. Anti-Sa antibodies belong to the family of anti-citrullinated protein/peptide antibodies. Antibodies directed to the Sa antigen are highly specific for RA. The antigen, a doublet of protein bands of about 50 KDa, is present in placenta and in RA synovial tissue. Auto-antibodies against the placental Sa antigen were described for the first time over a decade ago. Its prognostic value had already been shown to be better than that of anti-CCP and RF combined in early arthritis. Anti-Sa identifies a subset of male RA patients with severe disease.

Key words: Anti-Sa antibodies, Sa antigen, citrullinated vimentin, synovium prognosis, rheumatoid arthritis.

ÖZET

Özet: Romatid artrit (RA) ile ilişkilendirilen geniş bir oto-antikor grubu olduğu bilinmektedir. Araştırma tabanlı anti-Sa ELISA'nın duyarlılığı daha az olmasına rağmen anti-CCP ve RF'den daha özgül olduğu gösterilmiştir. Anti-Sa antikorları romatoid artrite yüksek özgüllük gösterip çoğunlukla IgG özelliğindedirler. Anti-Sa antikorları anti-sitrülinlenmiş protein/peptid antikor ailesine ait olup, Sa antijenine karşı yönlendirilen antikorlar romatoid artrite yüksek özgüllüğe sahiptirler. Yaklaşık 50 KDa ağırlığına sahip çiftli protein bantları halindeki antijen plasenta ve RA'de sinoviyal sıvı da gözlenmektedir. Plasental Sa antijenine karşı oto-antikorlar ilk kez yaklaşık on yıl önce tanımlanmışlardır. Erken artritte ki prognoz değeri beraber anti-CCP ve anti-RF değerlendirilmesinden daha iyi olduğu gösterilmiştir. Anti-Sa ağır seyre sahip erkek RA hastalarını tanımlamada önem taşımaktadır.

Anti-Sa antibodies, Sa antigen, citrullinated vimentin, synovium prognosis, rheumatoid arthritis.

Anahtar Kelimeler: Anti-Sa antikorlar, sitrülinlenmiş vimentin, sinovium prognozu, romatoid artirit.

Rheumatoid arthritis (RA) is characterized by the development of a persistent, destructive synovitis that targets multiple joints (1). Significant progress has been made in recent years towards understanding the specificity of autoimmune responses in RA, and the utility of auto-antibodies for diagnosis and outcome prediction in recent-onset arthritis. Many auto-antibodies directed against a variety of auto-antigens, can be detected in the serum of RA patients. Autoantibody screening in early arthritis cohorts may also prove useful for recruitment and selection of patients for clinical trials. Several additional auto-antibodies specificities have been studied in early RA. Anti-Sa antibodies were originally identified in a French Canadian patient with RA (2, 3).

The sensitivity of this antibody for RA varies with the stage of the disease tested (4). Immunologically, Sa is a hapten-carrier antigen in which vimentin is the carrier and citrulline is the hapten. The antigen, a doublet of protein bands of about 50 kDa, is present in placenta and in RA synovial tissue (3). Anti-Sa-antibodies therefore, belong to the family of anti-citrullinated protein antibodies. Anti-Sa antibodies are detected in the serum of 20-47% of patients with RA (5, 6). These antibodies have a high degree of specificity for the disease, and appear to identify a subset of early RA patients destined to have aggressive and destructive disease (7).

Many known auto-antibodies are directed against proteins that become modified during cell death and in particular during apoptosis (8, 9). These modifications include proteolytic cleavage by caspases or granzyme B, transglutamination, (de)phosphorylation, and also citrullination. The citrullination of vimentin is closely related to apoptosis, and citrullinated vimentin is extremely sensitive to digestion by the ubiquitous calpains. The Sa antigen is recognized by patients with high titers of anti-citrullinated protein antibodies. Of the anti-Sa-positive RA sera, most were also positive for anti-CCP. Of anti-Sa-negative RA sera, a considerable proportion was anti-CCP-positive, albeit at a lower titer. The anti-CCP titers of anti-Sa positive patients were on average more than three times as high as those of anti-Sa-negative RA patients (3, 10). When these modified self proteins are inefficiently cleared, they may be presented to the immune system and might be recognized as nonself. It has recently been confirmed that anti-Sa antibodies are directed to citrullinated vimentin, thus placing them in the anti-citrulline family of auto-antibodies. Vimentin is citrullinated in dying human macrophages. Furthermore, it has been reported that vimentin-derived citrullinated peptides were able to bind to HLA-DR4 shared epitope much more efficiently than non-citrullinated peptides (11, 12). The existence of citrullinated vimentin provided us with new clues to the nature of the Sa antigen (13).

The Sa antigen has previously been shown to be present in the synovium of 31-43% of patients with established RA, however, is present in only 20-25% of patients with early RA (14). Anti-Sa antibodies may play a pathogenetic role in the initiation and/or persistence of rheumatoid synovitis (15). At least 2 subsets of auto-antibodies are present in anti-Sa sera, one directed against a 68 kDa Sa protein and another to the typical 50/46 bands of the Sa system (16). These findings together with identification of the Sa antigen, make citrullinated vimentin an interesting candidate autoantigen in RA and may provide new insights into the potential role of citrullinated synovial antigens and the antibodies directed to them in the pathophysiology of RA (3).

Conclusion

The Sa antigen is present in the rheumatoid pannus. Anti-Sa antibodies have been described to be a highly specific marker for rheumatoid arthritis. The Sa antigen was suggested to be identical to citrullinated vimentin. The sera that is strongly positive for anti-CCP will score positive for anti-Sa. An association between anti-Sa-antibodies and disease severity has also been demonstrated. Anti-Sa antibodies are present from disease onset and are predictive of disease severity. The presence of anti-Sa antibodies appeared to be slightly more correlated with erosive disease outcome than the presence of anti-CCP.

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