Potential roles for tenascin in (very) early diagnosis and treatment of rheumatoid arthritis

We read the interesting article by Aungier *et al* suggesting that targeting proinflammatory signals from the C-terminal fibrinogen-like globe domain (FBG) of tenascin-C (TNC) might provide a viable strategy to treat rheumatoid arthritis (RA).[1]

The present story and possible developments are really interesting and might link to other recent evidences concerning the same argument.

We described for the first time in 1992 the distribution of TNC in normal and pathological synovial tissues from patients with RA and osteoarthritis (OA) by indirect immunofluorescence using specific monoclonal antibodies.[2]

Tenascin was found in normal synovium just beneath the whole lining cell layer; however, a higher density and spreading pattern of distribution was observed in RA and OA sections, but the possible meaning was unclear at that time.

Soon after, these early data were confirmed by others, and several investigations added that TNC levels were elevated in both RA cartilage and synovium and the T-C soluble form was detectable in synovial fluids of patients with RA.[3] Additionally, serum TNC levels were found to correlate with joint erosions in patients with RA.[4]

Interestingly, TNC stimulates inflammation by inducing de novo cytokine synthesis via activation of toll-like receptor 4 (TLR4), modulating cytokine synthesis post-transcriptionally via induction of microRNAs and regulating adaptive immunity by driving Th17 cell polarisation.[5 6] In murine models of arthritis, TNC expression is required to maintain chronic joint inflammation and, of note, the FBG of TNC is arthritogenic following its intra-articular injection.[7]

Here, the story offers important aspects.

Generally, anticitrullinated protein antibodies (ACPAs) are well-established markers for the diagnosis of RA, appearing before evident clinical symptoms and correlating with a poor prognosis and progressive joint destruction.[8]

However, very few molecules recognised by ACPA have been demonstrated in the joint, epitope-mapped, antigen specificity confirmed and evaluated in independent large cohorts.[8]

Among these, the most important recent TNC-related discovery was that a citrullinated peptide from the FBG domain of TNC (cTNC5) was detected in RA synovial fluids, and surprisingly antibodies to cyclic peptides containing citrullinated sites again from the FBG domain were found in both pre-RA and RA sera.[9]

In particular, the autoantibody response to the FBG immunodominant cTNC5 peptide was analysed in 101 pre-RA sera (median 7 years before disease onset) and two large independent RA cohorts. Interestingly, 18% of pre-RA sera, and in 47% and 51% of RA cohorts were found positive with a specificity of 98% compared with healthy controls and patients with OA.

In addition, FBG domain cTNC5 antibody levels were found the highest in the whole anti-CCP2 antibody-positive subgroup and even 4.9% of the patients with RA within the anti-CCP2 antibody-negative group were also anti-cTNC5 ACPA-positive. Therefore, the study suggested that the FBG domain of TNC may be important in both the aetiology and pathogenesis of RA.

The actual study of Aungier *et al* shows that monoclonal antibodies recognising the FBG of TNC neutralise the FBG activation of TLR4 and therefore inhibit cytokine release by RA synovial cells and prevent disease progression and tissue destruction during collagen-induced arthritis.

These results might really represent a new approach for (very) early RA therapy, by targeting early changes in the synovial microenvironment, especially in ACPA-positive patients.

In conclusion, testing the presence of anti-FBG cTNC in the sera of patients with early synovitis might help in discovering patients potentially developing RA, and might offer the chance of therapeutically targeting from the beginning the same FBG TNC domain with specific monoclonal antibodies.

This approach might block proinflammatory/immune signals from the extracellular matrix proteins (ie, tenascin) inside the synovial tissue, and from the beginning, as in a previous paper also some authors of the present study already recently tested and discussed.[10]

We agree with the authors that, on the light of these recent achievements, further explorations about potential roles of TNC in clinical practice for (very) early diagnosis and treatment of RA.

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