Autoimmunity Reviews 13 (2014) 1114–1120

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Anti-citrullinated peptides as autoantigens in rheumatoid arthritis—relevance to treatment

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ARTICLE INFO

Article history:
Received 14 July 2014
Accepted 21 July 2014
Available online 23 August 2014

Keywords:
Citrullinated antigens
Anticitrullinated antibodies
Rheumatoid arthritis
Autoantigens
Treatment

ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by the presence of rheumatoid factor (RF) and anti-citrullinated protein/peptide autoantibodies (ACPAs). Citrulline derives from arginine by peptidyl arginine deiminases, and ACPAs are directed against different citrullinated antigens, including fibrinogen, fibronectin, α-enolase, collagen type II, histones. ACPAs are present in two thirds of RA patients have higher specificity than RF for RA, and are associated with joint radiographic damage and extra-articular manifestations and they are detected years before the onset clinical arthritis. Recent studies suggest that citrullinated antigens are most likely arthritogenic autoantigens in RA. ACPA production is associated with the HLA-DRB1 shared epitope (HLA-DRB1 SE) and accounts for the well-known RA-HLA-DRB1 SE association, as T cells recognize citrullinated peptides. Smoking and periodontitis, known environmental risk factors for RA promote protein citrullination and ACPA production. Cirullinated proteins are capable of inducing arthritis in transgenic mice carrying HLA-DRB1 SE genes, and ACPAs induce macrophage TNF-α production, osteoclastogenesis and complement activation. They also induce the formation of neutrophil extracellular traps (NETs). NETs, increased in RA, are a source of citrullinated autoantigens in RA and induce fibroblast interleukin-8 production. This knowledge is likely to have therapeutic implications, as there is a need of matching therapy with patient profile. Abatacept, a T cell activation modulator, is the best therapy for ACPA(+) RA patients, although clinical data are sparse at present. Rituximab, a monoclonal antibody that depletes B cells, is also the best therapy for ACPA(+) RA patients, and clinical data support this view.

Contents

1. Introduction

The etiology of rheumatoid arthritis (RA) is not known. The concordance rate (up to 15%) of RA in monozygotic twins is low but higher than that in dizygotic twins (up to 5%) which suggests that in addition to genetic factors environmental factors also play an important role for the development of the disease [1,2]. The pathogenesis of RA is incompletely understood, but T cells have long been considered as

Abbreviations: ACPA, anti-citrullinated protein/peptide autoantibodies; APC, antigen presenting cells; CCP, cyclic citrullinated peptide; HLA-DRB1 SE, HLA-DRB1 shared epitope; IFN, interferon; IL, interleukin; NET, neutrophil extracellular trap; PAD, peptidyl arginine deiminase; RA, rheumatoid arthritis; RF, rheumatoid factor; TCR, T cell receptors; TLR, Toll-like receptor; TNF, tumor necrosis factor; Treg, T-regulatory.

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http://dx.doi.org/10.1016/j.autrev.2014.08.012
1568-9972/

main players for the development of the disease [3,4]. A T cell-centric concept of RA pathogenesis is in line with the heavy infiltration of RA synovial membrane with CD4+ T cells, the association of RA with HLA-DRB1 alleles, and the monoclonal/oligoclonal expansion of T cells from RA joints [5–9]. Because of the very large size of the T cell repertoire (2.5×10^7–1×10^8 different T cell receptors [TCRs]) [10], these clonal expansions cannot be explained by any other mechanism except that of involving proliferation and division of T cell in response to an antigenic epitope that they recognize [11].

2. HLA-DRB1 shared epitope and rheumatoid arthritis

In the late 1980s, RA was found to be associated with HLA-DRB1 alleles carrying a common amino acid sequence at positions 70–74 of the β chain, which has been known as HLA-DRB1 shared epitope (HLA-DRB1 SE) [12,13]. HLA-DRB1 SE alleles and in particular amino acids in position 70, as well as amino acids in positions 67, 71, and 74, form the important peptide binding pocket #4 in HLA-DRB1, which binds negatively-charged peptide side chains [14,15]. The HLA-DRB1 SE at positions 70–74, and in particular the Arg-Ala-Ala at position 72–74 is associated with high risk of developing RA. This risk is modulated by amino acids at positions 70–71; Gln or Arg at position 70 and Lys at position 71 confer the highest risk for developing RA [16–19]. Various researchers have tried to decipher the mechanism underlying the HLA-DRB1 SE association of RA. The shared epitope shares aminoacid homology with Epstein–Barr virus and could be a target of cross-reactive immune response by molecular mimicry. The HLA-DRB1*0401 QKRAA amino acid motif (shared epitope) is also present in the EBV glycoprotein gp110, and healthy controls with prior EBV infection have T cell recognizing the QKRAA motif [20,21]. Alternatively, HLA-DRB1 SE alleles may predispose to arthritis by shaping T cell repertoire in the thymus and activating autoreactive or deleting regulatory T cells (Tregs). In support of that transgenic mice carrying the RA-resistant HLA-DRB1*0402 had higher numbers of Tregs than mice carrying the RA-susceptible HLA-DRB1*0401 [22]. Given the well-known function of HLA-DR molecules, the RA association with HLA-DRB1 SE suggests that antigen presenting cells (APCs) carrying HLA-DRB1 SE alleles, present an arthritogenic peptide to T cells to initiate an immune response that results in a cytokine cascade with interferon(IFN)-γ, interleukin(IL)-17, tumor necrosis factor (TNF)-α, and IL-6 [3,4] (Fig. 1). What was still missing in this scenario was the identification of the arthritogenic peptide(s).

3. Citrullinated proteins as targets of B cells in rheumatoid arthritis

In the last 15 years, there has been considerable progress on the pathogenesis of RA with the discovery of anti-citrullinated protein antibodies (ACPAs). Citrulline derives from arginine by post-translational modification by peptidyl arginine deiminases (PADs). There are various isoforms of PADs, with PAD2 and PAD4 types being expressed in the RA synovium macrophages, and leukocytes, respectively [23,24]. There are few commercial tests for the detection of ACPA, including anti-cyclic citrullinated peptide (CCP) assays, and anti-mutated citrullinated vimentin test. The first generation of CCP1 assay used a cyclic derivative of a citrullinated filaggrin peptide. A second generation CCP2 and a third generation CCP3 assays contain multiple citrullinated epitopes in an attempt to increase sensitivity. It appears that CCP3 assays may have a higher sensitivity than CCP2 assays in early RA [25–29]. ACPA reactivity may be detected in non-RA sera, particularly in patients with autoimmune hepatitis and pulmonary tuberculosis, but often is due to the presence of antibodies that react with the uncitrullinated peptide target. Therefore, it is advisable that a positive CCP2 test in non-RA patients be followed by an uncitrullinated control antigen test [30,31].

ACPA are present in nearly two thirds of RA patients and are more specific than the rheumatoid factor for RA [32–34]. In an early meta-analysis, the pooled sensitivity and specificity of anti-CCP antibodies were 67% and 95%, respectively, the positive likelihood ratio was 12.46 and the negative likelihood ratio was 0.36 [35]. The respective figures for IgM rheumatoid factor were 69%, 85%, 4.86, and 0.38 [35]. ACPAs are also associated with the severity of the disease [34,36,37]. In fact, ACPAs are the strongest independent predictor of joint radiographic progression [38] and are associated with RA-interstitial lung disease [39]. ACPAs are more specific in diagnosing RA than rheumatoid factor (RF) [35] and are the best predictor of radiographic progression in early RA [33,40]. To this end, ACPAs are now included in the new classification criteria for RA [41,42] . Furthermore, ACPAs appearing up to 10 years before the onset of clinical RA [43,44], confer strong susceptibility to RA and predict the progression to RA in patients with undifferentiated arthritis [44–47]. ACPAs are directed against different citrullinated proteins, such as vimentin, histone, a-enolase, fibrinogen, fibronectin, filaggrin, collagen type II. ACPAs also recognize viral citrullinated peptides, such as citrullinated peptides derived from Epstein–Barr virus nuclear proteins EBNA1 and EBNA2 [25,48,49]. In fact, the accumulation of multiple ACPA specificities is correlated with preclinical inflammation (elevation of TNF-α, IL-6, and IFN-γ) preceding clinical arthritis [50]. Also, in the first degree relatives of RA patients without RA, the presence of >9 ACPA specificities was associated with increased risk of having >1 tender joint [51].

3.1. Citrullinated peptides as autoantigens in rheumatoid arthritis

The production of ACPAs is associated with HLA-DRB1 SE [25,44–46,49,52]. HLA-DRB1 SE alleles explain 18% of genetic variability of ACPA(+) RA but only 2.4% of ACPA(−) RA. Furthermore, HLA-DRB1 SE alleles influence the levels of ACPAs as RA patients carrying two HLA-DRB1 SE alleles have higher levels of anti-CCP antibodies than those carrying one HLA-DRB1 SE allele. In fact, the HLA-DRB1 SE is a risk factor for ACPA production and not an independent risk factor for the development of RA [49,53,54]. Cigarette smoking, which is a susceptibility and severity factor for RA [55–57], is also a strong inducer of protein citrullination. Tobacco exposure of transgenic mice carrying RA-susceptible HLA-DR alleles induces PAD [58] and is a risk factor for ACPA in RA patients carrying the HLA-DRB1 SE [59]. Periodontitis, an oral bacterial infection, is also associated with RA [60] as patients with periodontitis appear to have increased risk for RA [61,62] and inversely patients with RA have increased risk for periodontitis [63]. *Porphyromonas gingivalis*, a microbe that is the major causative agent for periodontitis, the only prokaryotic organism expressing PAD, can cause microbial and host protein citrullination [64].

ACPAs are of IgG or IgA isotype and, therefore, are most likely to require T cell help for their production. The association of ACPAs with the HLA-DRB1 SE re-enforces this concept. Recent studies have confirmed that ACPA production is T-cell-dependent. The conversion of arginine to citrulline in vimentin peptides dramatically increases the affinity of vimentin peptides for HLA-DRB1*0401 and is necessary for T cell activation [65]. Citrullinated vimentin peptides recognized by T cells from HLA-DRB1*0401 transgenic mice that were immunized with citrullinated vimentin peptides, are also recognized by T cells from ACPA(+), HLA-DRB1*04+ RA patients [66]. Similarly, the conversion of arginine to citrulline in fibrinogen peptides generated peptides that bound to pockets 4(P4), P7 and P9 of HLA-DRB1*1001, a SE allele [67]. Recently, a study by Scally et al. showed that the HLA-DRB1 SE alleles recognize citrullinated peptides in RA [68]. Citrulline was found within the electropositive P4 pocket of HLA-DRB1*04:01/04 (SE) alleles, whereas arginine interacted with electronegative P4 pocket of RA-resistant HLA-DRB1*04:02 allele. In addition, by the use of HLA-II tetramers, CD4(+) T cells recognizing citrullinated vimentin and citrullinated aggrecan were found in the peripheral blood of HLA-DRB1*04:01 RA patients and their number correlated with disease activity [68]. This piece of evidence is in line with another work showing that RA patients with ACPA exhibited very restricted TCR CDR3 length distribution in synovial biopsies, which reflected monoclonal/

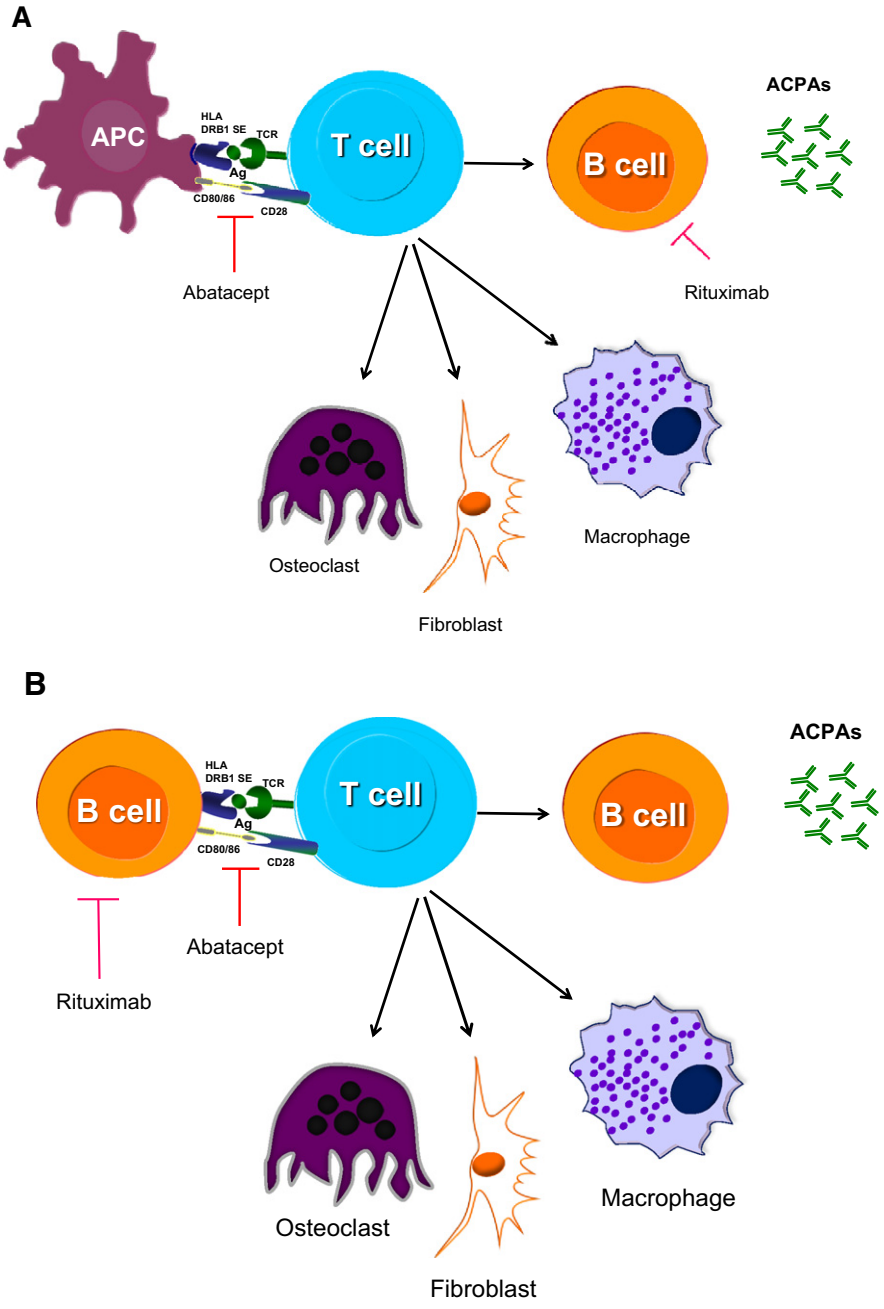

Fig. 1. T cell recognize through its T-cell receptor citrullinated peptide presented by HLA-DRB1 SE allele sitting on a professional antigen presenting cell (A) or on B-cell (B). This recognition sets up a cascade of interactions with other cells leading to synovial inflammation and articular bone loss. Abatacept (CTLA4-IgG) disrupts the CD28-CD80/CD86 interaction and dampens this autoimmune response very early. Rituximab, which depletes B cells also disrupts this autoimmune response very early. Therefore, abatacept and rituximab are likely to be more appropriate therapies for ACPA(+) patients with RA.

oligoclonal T cell expansions as determined by sequencing, in comparison to patients with ACPA(−) RA and to patients with spondylarthritis [69]. These differences were not observed in the peripheral blood of ACPA(+) versus ACPA(−) patients. These studies have shown that both T cells and B cell recognize citrullinated autoantigens in the context of a proper genetic background (HLA-DRB1 SE). Smoking appears to promote the production of ACPAs in RA patients carrying the HLA-DRB1 SE [70].

3.2. Arthritogenicity of citrullinated autoantigens

Citrullinated proteins and ACPAs are capable of inducting arthritis. Immune complexes containing citrullinated fibrinogen stimulated macrophage TNFα production via Toll-like receptor-4 (TLR4) and Fcγ receptor [71,72]. Citrullinated fibrinogen was also capable of macrophage TNFα production via TLR4 [72]. It appears that both citrullination of proteins and the HLA-DRB1 SE are required for the development of arthritis: citrullinated fibrinogen but not unmodified fibrinogen induced arthritis in transgenic mice carrying the RA-susceptible human HLA-DRB1 SE allele DRB1*0401. In contrast, citrullinated or unmodified fibrinogen could not induce arthritis in wild-type (B6) mice [73]. Citrullinated aggrecan peptide induced a proliferative response of peripheral blood mononuclear cells with proliferation of Th17 cells and interleukin-17 production in RA patients whereas non-citrullinated aggrecan peptide could not induce such a proliferation in healthy controls [74]. ACPAs enhance tissue injury in the collagen-induced arthritis model [75]. In another mouse model, antibodies against a citrullinated or uncitrullinated collagen type II epitope bind

to cartilage and synovial membrane and cause arthritis in mice [76]. The reduced severity of murine collagen-induced arthritis by a PAD inhibitor supports an arthritogenic (causing arthritis) role for citrullination and ACPA production in RA [77]. Similarly, *P. gingivalis* infection exacerbated collagen-induced arthritis (CIA), a finding that was dependent on the expression of *P. gingivalis* PAD [78]. However, an immune response to *P. gingivalis* could also induce ACPAs and arthritis. For instance, *P. gingivalis* α-enolase, either citrullinated or uncitrullinated can induce arthritis and anti-human citrullinated enolase antibodies in DR4-IE-transgenic mice [79]. It should be mentioned that there is a significant homology between human α-enolase and bacterial α-enolase, due to the conserved nature of the protein. In fact, in a citrullinated enolase peptide-1 which is a dominant B cell epitope, there is a 9 aminoacid span with 100% homology between human and α-enolase and *P. gingivalis* α-enolase [80], thus raising the issue of molecular mimicry between bacterial and host proteins as a mechanism for the break of tolerance in RA. ACPAs can induce damage by complement activation, as they activate complement in vitro, via both the classical and the alternative pathway, in a dose-dependent manner [81]. They can also induce osteoclastogenesis and bone loss [82]. Periarticular bone loss is a characteristic feature of RA. The association of smoking with joint damage is also attributed to ACPAs, since smoking is not an independent risk factor for joint damage [83]. Another mechanism by which ACPAs mediate their pro-inflammatory action may be through neutrophil extracellular traps (NETs). NETs, extruded from neutrophils during a form of necrosis called NETosis, are composed of decondensed chromatin and granule enzymes with antimicrobial properties. Enhanced NETosis was detected in RA sera and synovial fluid neutrophils and correlated with the presence of ACPA [84]. It should be mentioned that histone citrullination induced by PAD4 is a critical step in NETosis [85]. Citrullinated vimentin and citrullinated α-enolase are present in NETs formed spontaneously or in stimulated neutrophils from RA patients [84]. Citrullinated histone H4 present on NETs is also a target of autoantibodies in RA since anti-citrullinated H4 antibodies are detected in 67% of RA patients and their titer is correlated with anti-CCP2 [86]. Anti-citrullinated vimentin autoantibodies can induce NET formation while NETs induce fibroblast IL-8 production [84]. Therefore, NETs are a source of autoantigens in RA and vice versa ACPAs induce NET formation, thus promoting inflammation.

3.3. ACPA production in inflamed tissue

ACPAs can be produced in lymphoid organs or locally in the joints. Levels of ACPAs are elevated in synovial fluid compared with serum suggesting a local (in joints), production of these autoantibodies [48]. In the RA synovial membrane, intracellular citrullinated proteins were detected by immunostaining to be co-localized with PAD2 [87,88]. Indeed, using single B cell cloning technology, Amara et al. found that the majority of synovial membrane IgG-expressing B cells are specific for citrullinated autoantigens in ACPA(+) RA patients [89]. Another local site of ACPA may be the lungs. Bronchial tissue showed increased staining for citrullinated proteins in ACPA(+) compared with ACPA(−) patients with early RA. Furthermore, ACPA levels were higher in bronchoalveolar lavage fluid compared with sera of ACPA(+) patients with early RA [90]. Citrullinated proteins are also detected in periodontium tissue in RA patients with periodontitis [91].

Antigen-specific B cells, a source of autoantibodies, such as ACPAs, can function as non-professional APCs in RA. Unlike other APCs, B cells have an antigen receptor (B cell receptor, BCR) that recognizes a single antigen, either soluble and integrally part of a cell surface or located on extracellular matrix [92]. B cell antigen presentation is essential for T cell-dependent antibody production, such as IgG antibody production [93]. In primary biliary cirrhosis, a peptide from the E2 subunit of the pyruvate dehydrogenase complex (PDG-$E2_{212-226}$) is recognized by both B cells and T (CD4 and CD8) cells [94,95]. It is likely that ACPA-specific B cells can function as APC in RA (Fig. 1). In severe combined immunodeficiency mice with RA synovial membrane xenotransplantation, the activation of T cells requires B cells as APCs [9]. Therefore, it is expected that an agent that directly disrupt T cell–B cell interaction will decrease T cell activation and ACPA production in RA.

4. Optional therapy for ACPA(+) patients with rheumatoid arthritis

Could all this knowledge outlined above be translated into clinical practice? For instance, should ACPA(+) RA be treated differently than ACPA(−) RA? During the last 13 years a number of biological agents have been added to the armamentarium of RA treatment. These include tumor necrosis factor (TNF)-α inhibitors (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol), anti-B cell agent (anti-CD20, rituximab), anti-IL-6 receptor inhibitor (anti-IL-6R, tocilizumab), T cell modulator (CTLA4-IgG, abatacept). All these agents are effective therapies for RA [96]. In general, there is comparable effectiveness but the safety profile slightly differs among these agents [97]. A problem facing the practicing physician is to prescribe the most appropriate biological agent to individual patient, in other words, to match a biological agent with a patient profile, given the high cost of biologicals [98]. One study has reported that the presence of ACPAs was associated with reduced response to anti-TNFα agents [99]. Abatacept, a cytotoxic T lymphocyte-associated antigen 4-Immunoglobulin (CTLA4-IgG) fusion construct, blocks the CD28 (on T cells)-CD80/CD86 interaction and modulates T cell activation [100]. B cells can function as non-professional antigen presenting cells, express CD80/CD86 molecules and signaling through CD80/CD86 enhances IgG secretion in previously activated (class-switched) B cells [101]. Therefore, it is logical to assume that abatacept would downregulate T cell activation and ACPA-specific B cells as well, and it would be more efficacious treatment for ACPA(+) RA patients. Clinical data support this notion. Abatacept treatment in RA patients reduces CD20(+) B cells in the synovial membrane [102,103]. It also significantly reduces the production of IL-2, IL-17, IL-22 in ACPA(+) but not in ACPA(−) RA patients [104]. The latter study fits nicely with a multivariate analysis of data from the French Orencia (abatacept) registry showing that in patients with RA, anti-CCP positivity was associated with EULAR response (odds ratio = 1.9, CI = 1.2 to 2.9) and a higher abatacept survival rate [105]. These results may point towards the concept that abatacept is more efficacious in ACPA(+) RA patients.

Rituximab, a monoclonal antibody that deletes B cells [106] also appears to be the most appropriate therapy for ACPA(+) RA patients. In a multivariate analysis in RA, ACPA positivity or high ACPA levels were associated with good to moderate EULAR response to rituximab [107–110]. In pooled data from 10 European RA registries, predictors of good EULAR response were ACPA positivity and not RF positivity [111]. Anti-CCP antibody levels after rituximab therapy in RA fall in responders relative to non-responders [112].

It should be mentioned that current assays available in a clinical setting detect antibodies against cyclic citrullinated peptides but do not detect all ACPAs. Using a multiplex assay based on citrullinated antigens that are present in RA joints, Wagner et al. detected at least 10% more ACPA(+) in RA patients who were ACPA(−) by an anti-CCP2 assay [113]. In addition, new anti-citrullinated collagen type II antibodies, which bind to human cartilage, were detected in 21% of RA patients [114]. With the advent and the increasing availability to the clinical laboratory of new more sensitive assays for IgG/IgA ACPA testing, it is anticipated that the true advantage of abatacept or rituximab therapy in ACPA(+) RA patients will be fully elucidated.

Take-home messages

- ACPAs are associated with HLA-DRB1 SE and account for the known association of RA with HLA-DRB1 SE.
- Citrullinated antigens are recognized by B cells and T cells.
- Citrullinated antigens appear to be arthritogenic.
- ACPAs induce macrophage TNF production and NET formation.
- Rituximab and most likely abatacept are best suited for the treatment of ACPA(+) RA patients.

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