Anticyclic citrullinated peptide antibodies: the footprint of autoreactive plasma cells in synovium?

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The presence of circulating anticyclic citrullinated protein antibodies (ACPAs) is a very specific finding in patients with rheumatoid arthritis (RA). A key question is whether ACPAs are pathogenic autoantibodies or merely bystander products. While studies have demonstrated local production of ACPAs in inflamed tissues, it has not yet convincingly been shown that ACPAs are indeed pathogenic autoantibodies, especially not when put in perspective of other known pathogenic autoantibodies. Autoantibodies are produced by plasma cells and it has long been known that plasma cell infiltration in synovium is commonly found in RA patients. In this review we summarize the evidence that (autoreactive) plasma cells may be involved in RA. A better understanding of the biology of plasma cells in RA may open new avenues for treating RA.

Keywords: anticyclic citrullinated peptide antibodies (ACPAs), plasma cells, rheumatoid arthritis, synovium

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Autoimmune diseases are chronic inflammatory illnesses of unknown etiology, commonly accompanied by the presence of circulating autoantibodies [1]. A returning subject of many investigations is the question of whether autoantibodies are pathogenic or merely bystander products of an abnormal immune response. Criteria have been proposed to determine whether an autoantibody is pathogenic [2]. First, a plausible mechanism of action is required for autoantibodies to be called pathogenic. Second, pathogenic autoantibodies should be capable of causing the lesions attributed to autoimmune disease. Third, immunization should lead to the production of similar autoantibodies and eventually to a similar disease process. Fourth, pathogenic autoantibodies should be found along with the putative autoantigen at the site of tissue inflammation. Fifth, autoantibody levels and disease activity should correlate. And last, the removal of the autoantibodies, when possible, should ameliorate the disease process.

In the present review, the significance of autoantibodies directed against citrullinated proteins (ACPAs) in patients with rheumatoid arthritis (RA) is discussed in the context of the criteria mentioned above. We particularly focus on a possible pathogenic role for autoreactive plasma cells in RA as the cellular origins of autoantibodies, viewed in a wider context of autoantibody-mediated conditions.

Scope on pathogenic autoantibodies

RA is a systemic autoimmune disease characterized by symmetrical joint involvement due to synovial inflammation, leading to joint erosion and deformities [1]. Since the identification of citrullinated epitopes [3] as a target for several autoantibodies found in RA patients, many reports have demonstrated that ACPAs are a specific finding in RA patients [4–8]. The biological and immunological relevance of ACPA remains to be determined, however. In this regard, it is useful to briefly consider other autoantibodies that are generally accepted to be involved in disease pathogenesis. Examples of pathogenic autoantibodies are summarized in **Table 1**. Below, we briefly expand on antiepidermal antibodies in pemphigus, an organ-specific autoimmune disease characterized by generalized blistering of the skin [9], and autoantibodies against double-stranded DNA in systemic lupus erythematodes (SLE) [10]. These autoantibodies were chosen to illustrate current concepts about their pathogenecity in view of the previously described criteria.

In pemphigus (foliaceus and vulgaris types), autoantibodies against desmoglein play a major role in the induction of the blistering of skin and mucous membranes through the loss of intracellular adhesion [11]. Studies using direct immunofluorescence have shown that immunoglobulins are bound to the epidermal cell surface in virtually all patients [9]. Passive transfer of serum from patients led to acantholysis in epidermal cell cultures and transfer to neonatal mice reproduced blistering disease, clinically, histologically and immunologically [12,13]. The observation that disease could also be passively transferred by Fab-fragments of antiepidermal antibodies indicated that the mere binding of the autoantibodies to the desmoglein target was sufficient for induction

Table 1. Overview of systemic and organ-specific autoimmune diseases and their pathogenic autoantibodies.*

Autoimmune diseases	Target organ(s)	Target(s) of pathogenic autoantibody*
Rheumatoid arthritis	Joints	Citrullinated proteins, rheumatoid factor
Systemic lupus erythematosus	Systemic	Double stranded DNA, nuclear residues: SSA/Ro, SSA/La, phospholipids
Sjogren's syndrome	Salivary gland	Nuclear residues: SSA/Ro, SSA/La
ANCA-associated vasculitis	Vasculature	Myeloperoxidase (MPO) and proteinase 3 (PR3)
Antiphospholipid syndrome	Vasculature	Phospholipids
Idiopathic thrombocytopenia	Platelets	Platelets
Guillain–Barre syndrome	Peripheral nervous system	Myelin, monosialoganliosides
Autoimmune thyroiditis	Thyroid gland	Thyroid-stimulating hormone (TSH) receptor
Pemphigus vulgaris	Skin, mucous membranes	Desmoglein
Myasthenia gravis	Skeletal muscle	Acetylcholine receptor
Type I diabetes	Pancreatic islet cells	Pancreatic islets of Langerhans
Addison's disease	Adrenal gland	21-hydroxylase enzyme
Goodpasture's syndrome	Lung, kidney	Glomerular basal membrane (GBM)
Pernicious anaemia	Stomach	Parietal cells, intrinsic factor
Primary biliary cirrhosis	Liver	Mitochondrial autoantigens
Dermatomyositis-polymyositis	Skeletal muscle, skin	Aminoanyl tRNS synthetase, signal recognition particle (SRP), nuclear helicase (Mi-2)
Celiac disease	Small intestine	Gliadin, endomysium (tissue transglutaminase)

**Autoantibodies that are currently considered to associate with the etiology of their corresponding disease but not necessarily fulfil all the criteria for pathogenecity.*

ANCA: Antineutrophil cytoplasmic antibody; tRNS: Transfer-reactive nitrogen species.

of disease [14]. Moreover, children of mothers with pemphigus may develop transient disease due to maternal antibodies crossing the placenta [15,16]. The level of antidesmoglein antibodies correlates with disease activity [17] and the removal of these antibodies by plasmapheresis leads to clinical improvement [18]. Additionally, newer therapies, such as treatment with anti-CD20 monoclonal antibodies, have recently been shown to be clinically effective and reduce antidesmoglein autoantibody levels [19,20]. Altogether, there is convincing evidence that antidesmoglein antibodies are the pathogenic source of pemphigus disease, even though it is controversial whether antidesmoglein autoantibodies in themselves directly cause the loss of adhesion [9].

In SLE, generally viewed as the prototype systemic autoimmune disease, there is supporting evidence for a pathogenic role of several autoantibodies, including anti-DNA autoantibodies, anti-Ro antibodies and antiphospholipid antibodies. Recent studies have demonstrated the arrhythmogenic potential of anti-Ro autoantibodies [21–23]. Also, the close epidemiologic association between antiphospholipid autoantibodies and thrombosis [24] has been experimentally corroborated showing that these autoantibodies were associated with a significant increase in thrombus size and a delay in thrombus dissolution [25]. However, the largest body of evidence has been produced on autoantibodies against double-stranded DNA (anti-dsDNA antibodies) based on the correlation of circulating levels of anti-dsDNA autoantibodies with disease activity [26,27]. Furthermore, the combination of high anti-dsDNA levels and consumption of complement factors are diagnostic for SLE [10]. In addition, anti-dsDNA autoantibodies were demonstrated to bind directly to the glomerular basement membrane of the kidneys [28], linking these autoantibodies to the pathogenesis of lupus nephritis. However, it is unclear whether the anti-dsDNA autoantibodies bind directly to the glomerular membrane or are deposited in the membrane through immune complex formation. Passive transfer of lymphocytes from lupus patients to severe combined immune-deficient (SCID) mice did not induce glomerulonephritis, although antinuclear antibodies and deposition of IgG and complement in the kidney could be detected [29,30]. Importantly, the clinical outcome in SLE patients with severe nephritis did not improve after plasmapheresis [31,32]. The merit of B-cell-depleting therapies is currently being investigated [33,34]. Recently, Anolik *et al.* reported that

rituximab treatment did not eliminate anti-dsDNA autoantibodies in all SLE patients [35]. Overall, it can be concluded that anti-dsDNA autoantibodies are related to nephritis in SLE patients, but may not in themselves explain all SLE-related symptoms.

In summary, only a limited number of autoantibodies will meet the criteria for being pathogenic, of which the antidesmoglein autoantibody in pemphigus seems to fulfill most criteria. In systemic autoimmune diseases in particular, autoantibodies alone do not explain all clinical symptoms.

A pathogenic role for ACPAs in RA?

ACPAs are directed against the citrulline residue of citrullinated proteins. Citrulline is an amino acid that is not incorporated into proteins during mRNA translation but can be generated by post-translational modification of arginine residues by peptidylarginine deaminase (PAD-) enzymes [36]. Therefore, an intrinsic characteristic of ACPAs is the recognition of different peptides containing citrulline, such as citrullinated fillagrin (i.e., antiperinuclear factor [APF] and antikeratin autoantibodies [AKA], collectively named anti-fillagrin autoantibodies) [37] and citrullinated vimentin (anti-Sa) [38]. Citrullination of extracellular proteins such as fibrin, which is commonly present in chronically inflamed joints, can occur when PAD-enzymes are released from cells that undergo apoptosis, also a common process in inflamed synovium [39]. Several studies have reported the presence of citrulline residues and ACPAs in synovium [5,40]. Moreover, two studies demonstrated the production of ACPAs in synovial explants [41,42], while other reports showed higher levels of ACPAs in synovial fluid as compared with serum [39,43–45]. Collectively, these studies clearly indicate that ACPAs are present at the site of inflammation in RA patients (although not excluding other sources) and that they are targeted against antigens generated through a plausible mechanism.

However, whether ACPAs themselves can cause tissue inflammation and erosive disease in RA patients remains to be determined. It has been demonstrated in several studies that RA patients with ACPAs had a more progressive disease [46–49], at least suggesting a role of ACPAs in joint destruction. A recent study showed a moderate correlation between ACPA levels and radiological erosion scores [50], but an association between ACPA levels and disease activity has not yet been found [51]. Additionally, elimination of ACPA by plasmapheresis has not been reported. Still, it is intriguing that the presence of ACPAs was demonstrated years before symptoms of joint inflammation became clinically overt [52,53]. Also, in a collagen-induced arthritis model, ACPAs were demonstrated before the development of experimental arthritis and induction of tolerance for citrulline was associated with lower disease severity [54]. These reports indicate that the presence of ACPAs in serum is intrinsically related to clinical symptoms of arthritis.

Further support for the pathogenic role of ACPAs in RA can be deduced from studies evaluating ACPA levels in effectively treated RA patients. Of special interest is the recent introduction of B-cell-depleting therapies in RA. Treatment with rituximab, an anti-CD20 monoclonal antibody, was shown to be clinically effective in RA [55–57] and an increase in ACPA levels after treatment preceded clinical relapse [58]. However, several reports demonstrated only moderate effects on ACPA levels despite good clinical effects [59,60]. Along the same lines, TNF-blocking agents resulted in significant improvements of disease activity but, although controversial, the majority of studies did not show large reductions of circulating ACPA autoantibodies [8,61–64]. Also for conventional DMARD treatment, reduction in levels of circulating ACPAs were modest albeit statistically significant [65]. Taken together, these studies show that a reduction or eradication of ACPAs is not a prerequisite for clinical improvement of RA, and it remains unknown whether ACPAs are responsible for the chronicity of RA symptoms.

In summary, there is ample evidence that ACPAs can be detected and are produced at the site of joint inflammation in RA patients. ACPAs are specific for RA and are associated with disease progression and a worse outcome. However, firm evidence that ACPAs themselves are pathogenic agents in the disease processes of RA patients still needs to be provided. As a consequence, it is evident that the cellular origin of autoantibodies, for instance, autoreactive plasma cells, needs closer attention, especially because the production of ACPAs remains a very specific finding in RA patients.

Synovial plasma cell infiltration is related to disease activity in RA

Because ACPAs are produced by (autoreactive) plasma cells, it is logical to assume that plasma cells have a role in RA pathogenesis. Although no study has yet reported the existence of

ACPA-specific producing plasma cells (probably due to technical limitations), several studies independently reported that plasma cells are a specific finding in the synovium of RA patients. The presence of plasma cells in synovial biopsies of arthritic patients was observed to have a specificity of 72% for RA diagnosis [40] and a high degree of plasma cell infiltration was able to correctly diagnose RA in approximately 85% of patients with early arthritis [66,67]. Moreover, RA synovium showed a gradual increase in plasma cell infiltration when developing from an acute to subacute and finally chronic synovitis [68]. Overall, these data indicate that plasma cell infiltration is a very specific finding for RA, notably in chronic, longstanding disease. It is therefore worthwhile to consider the body of evidence concerning the role of plasma cells in the pathogenesis of RA, as summarized below.

When addressing plasma cell biology, it is important to realize that the immunobiology of life-long humoral immunity against pathogens in man is still the subject of continuous debate [69,70]. Two concepts are currently competing, but not mutually exclusive: in the first model, memory is mediated through polyclonal bystander activation of memory B-cells leading to maintenance of serum antibody concentrations of various antigen specificities [70]. In the second model, memory depends on the continuous competition for survival niches between newly formed plasma cells and 'older', resident plasma cells [69]. The concept of survival niches is supported by a vast array of studies showing that the survival and function of plasma cells is dependent upon their environment [71–74]. Nevertheless, our understanding of the physiological processes that govern the homeostasis of plasma cells is still poor and, consequently, their role in autoimmune disease is even less well defined. Therefore, in order to clarify the possible relationship between synovial plasma cell infiltration and RA pathogenesis, we approached this issue by answering the following pivotal questions: a) is inflamed synovium an adequate survival niche for plasma cells? b) as plasma cells can specifically be found in RA patients, can plasma cells either be generated locally or migrate into inflamed synovium? and c) does adequate, immunosuppressive treatment for RA also have detrimental effects on synovial plasma cells?

First, to demonstrate that inflamed synovium is an adequate survival niche, it is important to know that there is a wide array of studies showing that several signals, alone or in synergism, can support the survival of plasma cells in bone marrow [72,75,76]. These signals include, among many more, chemokine receptor-ligand-12 (CXCL-12), TNF, IL-5, IL-6, B-lymphocyte activating factor (BAFF) and a proliferation-inducing ligand (APRIL), all produced in high concentrations in inflamed tissues. Not surprisingly, plasma cells can be found at a high degree in inflamed synovium of RA patients [40,66]. It has been reported that the immune response against recall antigens elicited by lymphocytes from inflamed synovial tissue is skewed when compared with the lymphocytes in peripheral blood [77,78], suggesting that cellular infiltrates are composed of a selected population of, including possibly autoreactive, plasma cells. Overall, it is well-established that inflamed synovium of RA provides a survival niche for autoreactive plasma cells [79].

Second, an important issue in unraveling the pathogenic contribution of synovial plasma cells in RA is to determine whether these plasma cells have been generated locally, in inflamed synovium, or have migrated from lymphoid organs to the site of inflammation, or both. In mice, autoreactive plasma cells were shown to survive in virtually every lymphoid organ, including spleen, bone marrow and inflamed tissue. In NZB/W mice, a model for SLE, long-lived (nondividing) as well as short-lived (dividing) autoreactive plasma cells could be observed in spleen, inflamed kidney and bone marrow of these mice [80]. In collagen-induced arthritis, production of anticollagen autoantibodies was demonstrated in lymph nodes, bone marrow as well as arthritic paws [81]. In humans, several studies have demonstrated the formation of large T-cell–B-cell aggregates with incidental co-localization of CD21L+ follicular dendritic cells in inflamed synovial tissue [82–85], resembling germinal center-like structures. Because the differentiation to the stage of plasma cell is dependent upon CD70/CD27 interactions [86,87], the close interaction between T cells and B cells support the hypothesis that plasma cells can be locally formed. Moreover, memory B cells can be locally generated through the close interaction with T cells via CD40–CD154 interactions [88,89]. Both mechanisms create the possibility for local, most likely autoantigen-driven, generation and differentiation of plasma cells. Arguments against the local formation of autoreactive plasma cells in synovium came from studies suggesting that CXCR4 expression on early plasma cells is important for the migration of these cells

from lymphoid organs to bone marrow and inflamed tissue [90–92], supporting the view that early plasma cells migrate to the site of inflammation. However, it has not yet been shown that terminally differentiated plasma cells also migrate towards inflamed synovium. In this regard, a recent study described the penetration of the cortical barrier by synovial inflammatory cells at the junction zone (i.e., the insertion site of the synovial membrane into the articular cartilage and periosteum) [93]. This finding raised the possibility that terminally differentiated plasma cells are able to migrate directly from bone marrow to the inflamed synovium or *vice versa*. Indeed, this study showed that mature B cells were the predominant cell type of these periosteal cell infiltrates and found that plasma cells were enriched in this region [93], but were unable to determine whether terminally differentiated plasma cells actually migrated into the synovium. On the whole, the issue of the origin of synovial plasma cells remains unresolved.

Third, our understanding of the pathologic contribution of plasma cells in RA has been augmented by recent data on the effects of immunosuppressive treatment on the infiltration of plasma cells in synovium. Importantly, local formation of plasma cells in inflamed synovium implies that these plasma cells are proliferating cells or dependent upon proliferating cells, making them more susceptible to immunosuppressive treatment than in the case of migration of matured, terminally differentiated plasma cells. Several studies have reported the effects of different antirheumatic treatments on the cellular infiltration in synovium. One study reported on the clinical and biological effects of high-dose chemotherapy (HDC) followed by autologous hematopoietic stem cell transplantation (HSCT) [94]. In the responders to HDC + HSCT, the intensive antiproliferative and immunosuppressive treatment led to reductions in all markers of the synovial cellular infiltrate, including synovial $CD138^+$ plasma cells [94]. Importantly, responsiveness to HDC + HSCT was associated with extensive synovial inflammation before treatment and significant reductions of low-avidity ACPA autoantibodies from the circulation [95]. The latter suggested an association between reduction of synovial plasma cells and the reduction of ACPA autoantibodies. Similarly, TNF-blocking agents significantly reduced $CD38^+$ plasma cells in synovium from patients, naive or refractory to conventional DMARDs. In this study $CD38^+$ $CD138^+$ double-positive plasma cells were more susceptible to TNF-blocking therapy than activated T cells that were double positive for CD38 and CD3 [96]. Another study evaluating the synovial effects of TNF-blocking agents versus placebo treatment confirmed reductions in $CD38^+$ plasma cells, but also reported significant reductions in intimal macrophages [97]. This was also reported by Gerlag *et al.* demonstrating that oral corticosteroids led to significant reductions not only of sublining macrophages notwithstanding but also of $CD38^+$ cells, presumably plasma cells [98]. These studies illustrate the close relationship between changes in plasma cells and disease activity brought about by immunosuppressive treatments.

It is noteworthy that the abovementioned treatments (DMARDs, corticosteroids, chemotherapy or TNF-blocking agents) not only target plasma cells, and consequently the observed reductions could merely reflect broad suppression of inflammation. It has already been stated that the survival of plasma cells depends upon environmental conditions. The introduction of cell-targeted therapies with anti-CD20 monoclonal antibodies has recently provided intriguing findings with regard to synovial plasma cells. Two studies investigating the effects of anti-CD20 monoclonal antibodies (rituximab) in synovium demonstrated a reduction in synovial plasma cells after treatment. However, one of these studies showed that the reduction of synovial plasma cells was not a direct effect but a delayed result of local $CD20^+$ B-cell depletion [99,100]. Importantly, the infiltration of plasma cells, expressing $CD79a^+$ but not CD20 or CD138, predicted the responsiveness to rituximab treatment in these patients [59]. Collectively, these studies indicate that the survival of plasma cells in synovium, irrespective of them being produced locally or migrating into the synovium, is closely associated with the response to antirheumatic treatments.

ACPAs: the footprint of plasma cell activation in synovium

Currently, there is little evidence supporting a direct relationship between circulating ACPA levels and disease activity in RA patients. On the other hand, several studies have demonstrated that elimination of plasma cells in synovium is associated with improvement of disease activity. The latter has not been the case for ACPAs, as it is still unclear why antirheumatic therapies (DMARDs and biologicals) are unable to eliminate ACPA production despite the clinically

observed improvements. Together with the observation that synovial infiltration of plasma cells is characteristic for RA patients this argues in favor of the hypothesis that ACPA producing cells, not ACPAs themselves, play a prominent role in RA.

This hypothesis does not claim that autoreactive plasma cells are the causative cell population for RA. Obviously, the development of long-lived plasma cells is dependent upon T-cell dependent B-cell activation and plasma cell survival is largely dependent upon interaction with the local environment, through soluble factors (cytokines, chemokines) or cell–cell or cell–matrix contact. In a study by Tak *et al.* on the histological effects of anti-CD4 treatment (cM-T412), in patients whose $CD4^+$ T cells were eliminated (and thus also $CD3^+$ T cells), a simultaneous reduction of synovial $CD38^+$ plasma cells could be seen [101]. These results strongly suggested that the survival of synovial plasma cells is T-cell dependent. This is in accordance with recent observations on plasma cell survival in human tonsils [102]. However, although plasma cells may not be the sole dysfunctional cell population in RA, it is well appreciated that they can play an important role in the perpetuation of autoimmune disease. Therefore, the assignment of a central role to autoreactive plasma cells in the disease process of RA patients leads to a shift in focus of ACPA-related investigations from questioning ACPA's pathogenicity to unraveling the mechanisms leading B cells to differentiate into autoreactive, ACPA-producing plasma cells. Consequently, the fate of these developed autoreactive plasma cells is of high interest. For example, it is as yet unknown whether ACPAs are produced in bone marrow and other lymphoid tissues of RA patients.

Thus, the role of autoreactive, ACPA-producing plasma cells in the pathogenesis of RA remains to be elucidated. It is known that TGF-β mRNA can be expressed by human bone marrow plasma cells [103], which is known to regulate proliferation, differentiation and other functions in most cell types. Through the production of cytokines, such as TGF-β, plasma cells may exert some not yet recognized immunoregulatory functions. Also, plasma cells express and actively produce the proteolytic matrix metalloproteinases (MMPs), notably MMP-3 and MMP-9 [104]. Because MMPs play a pivotal role in tissue remodelling, local infiltrated plasma cells in synovium might be capable of mediating destructive processes characteristic for RA. Additionally, it was recently shown that plasma cells expressed Fcγ-receptor IIB (FcγRIIB), through which their survival is regulated. It was also reported that survival of autoreactive plasma cells was prolonged in a mouse model for SLE due to the loss of FcγRIIB expression [105]. It is conceivable that similar mechanisms are operative in inflamed synovium of RA patients.

Executive summary

The role of anticyclic citrullinated protein antibodies in rheumatoid arthritis

- Anticyclic citrullinated protein antibodies (ACPAs) are very specific for rheumatoid arthritis and produced at the site of joint inflammation.
- RA patients seropositive for ACPA have more severe RA.

ACPA in perspective

- When compared with other well-established autoantibody-mediated diseases (pemphigus, systemic lupus erythematodes) the current evidence in favor of ACPAs being pathogenic autoantibodies in RA is pending.

The emerging role of autoreactive plasma cells in RA

- Because ACPA production is a very specific finding in RA, ACPA producing plasma cells are increasingly being considered as part of the pathologic processes involved in RA.
- Several studies have established a close relationship between synovial infiltration of plasma cells and disease severity in RA patients.

Conclusion

- Although our understanding of plasma cell biology is still developing, autoreactive plasma cells are potential key players in the maintenance and perpetuation of RA.
- ACPAs may prove to be the footprint of pathologic mechanisms sustaining autoreactive plasma cells in RA patients.

Future perspective

- Unraveling the differences in plasma cell biology between healthy individuals and RA patients will augment our understanding of disease processes in RA. This may lead to new therapeutic strategies.

Future perspective

In conclusion, plasma cells may prove to have a more central role in RA pathogenesis than is currently appreciated. The pathological mechanisms involved in the formation and survival of autoreactive plasma cells in RA are largely unknown. For example, while the isotype distribution and the avidity of circulating ACPAs can vary between patients, it is thus far unknown whether the underlying mechanisms for isotype switching and affinity maturation of ACPA-producing cells resemble those of regular antibody-producing cells. Further studies are needed to identify the immunobiology of autoreactive plasma cells. The results of such studies may lead to new and effective treatments to achieve long-lasting control of disease activity in RA.

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC. In: *Oxford Textbook of Rheumatology* (*3rd Edition*) Oxford University Press, UK (2005).
2. Naparstek Y, Plotz PH: The role of autoantibodies in autoimmune disease. *Annu. Rev. Immunol.* 11, 79–104 (1993).

•• **Reviews the criteria for pathogenecity of autoantibodies.**

3. Schellekens GA, de Jong BA, van den Hoogen FH, van de Putte LB, van Venrooij WJ: Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. *J. Clin. Invest.* 101(1), 273–281 (1998).

• **Demonstrated citrullinated protein as the common epitope recognized by several rheumatoid arthritis/specific autoantibodies.**

4. van Gaalen FA, Visser H, Huizinga TW: A comparison of the diagnostic accuracy and prognostic value of the first and second anti-cyclic citrullinated peptides (CCP1 and CCP2) autoantibody tests for rheumatoid arthritis. *Ann. Rheum. Dis.* 64(10), 1510–1512 (2005).
5. Mimori T: Clinical significance of anti-CCP antibodies in rheumatoid arthritis. *Intern. Med.* 44(11), 1122–1126 (2005).
6. Samanci N, Ozdem S, Akbas H *et al.*: Diagnostic value and clinical significance of anti-CCP in patients with advanced rheumatoid arthritis. *J. Natl Med. Assoc.* 97(8), 1120–1126 (2005).
7. Gao IK, Haas-Wohrle A, Mueller KG, Lorenz HM, Fiehn C: Determination of anti-CCP antibodies in patients with suspected rheumatoid arthritis: does it help to predict the diagnosis before referral to a rheumatologist? *Ann. Rheum. Dis.* 64(10), 1516–1517 (2005).
8. Kastbom A, Strandberg G, Lindroos A, Skogh T: Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). *Ann. Rheum. Dis.* 63(9), 1085–1089 (2004).
9. Stanley JR, Amagai M: Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. *N. Engl. J. Med.* 355(17), 1800–1810 (2006).
10. Swaak T, Smeenk R: Clinical significance of antibodies to double stranded DNA (dsDNA) for systemic lupus erythematosus (SLE). *Clin. Rheumatol.* 6(Suppl. 1), 56–73 (1987).
11. Amagai M: Pemphigus: autoimmunity to epidermal cell adhesion molecules. *Adv. Dermatol.* 11, 319–352 (1996).
12. Roscoe JT, Diaz L, Sampaio SA *et al.*: Brazilian pemphigus foliaceus autoantibodies are pathogenic to BALB/c mice by passive transfer. *J. Invest. Dermatol.* 85(6), 538–541 (1985).
13. Amagai M, Karpati S, Prussick R, Klaus-Kovtun V, Stanley JR: Autoantibodies against the amino-terminal cadherin-like binding domain of pemphigus vulgaris antigen are pathogenic. *J. Clin. Invest.* 90(3), 919–926 (1992).
14. Rock B, Labib RS, Diaz LA: Monovalent Fab' immunoglobulin fragments from endemic pemphigus foliaceus autoantibodies reproduce the human disease in neonatal Balb/c mice. *J. Clin. Invest.* 85(1), 296–299 (1990).
15. Wasserstrum N, Laros RK Jr: Transplacental transmission of pemphigus. *JAMA* 249(11), 1480–1482 (1983).
16. Avalos-Diaz E, Olague-Marchan M, Lopez-Swiderski A, Herrera-Esparza R, Diaz LA: Transplacental passage of maternal pemphigus foliaceus autoantibodies induces neonatal pemphigus. *J. Am. Acad. Dermatol.* 43(6), 1130–1134 (2000).
17. Sams WM Jr, Jordon RE: Correlation of pemphigoid and pemphigus antibody titres with activity of disease. *Br. J. Dermatol.* 84(1), 7–13 (1971).
18. Roujeau JC: Plasmapheresis therapy of pemphigus and bullous pemphigoid. *Semin. Dermatol.* 7(3), 195–200 (1988).
19. Joly P, D'Incan M, Musette P: Rituximab for pemphigus vulgaris. *N. Engl. J. Med.* 356(5), 521–522 (2007).
20. Ahmed AR, Spigelman Z, Cavacini LA, Posner MR: Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N. Engl. J. Med.* 355(17), 1772–1779 (2006).
21. Eftekhari P, Salle L, Lezoualc'h F *et al.*: Anti-SSA/Ro52 autoantibodies blocking the cardiac 5-HT4 serotoninergic receptor could explain neonatal lupus congenital heart block. *Eur. J. Immunol.* 30(10), 2782–2790 (2000).
22. Kamel R, Eftekhari P, Clancy R, Buyon JP, Hoebeke J: Autoantibodies against the serotoninergic 5-HT4 receptor and congenital heart block: a reassessment. *J. Autoimmun.* 25(1), 72–76 (2005).
23. Wahren-Herlenius M, Sonesson SE: Specificity and effector mechanisms of autoantibodies in congenital heart block. *Curr. Opin Immunol.* 18(6), 690–696 (2006).
24. Galli M, Barbui T: Antiphospholipid antibodies and thrombosis: strength of association. *Hematol. J.* 4(3), 180–186 (2003).
25. Pierangeli SS, Liu XW, Barker JH, Anderson G, Harris EN: Induction of thrombosis in a mouse model by IgG, IgM and IgA immunoglobulins from patients with the antiphospholipid syndrome. *Thromb. Haemost.* 74(5), 1361–1367 (1995).
26. Sjoholm AG, Martensson U, Sturfelt G: Serial analysis of autoantibody responses to the collagen-like region of Clq, collagen type II, and double stranded DNA in patients with systemic lupus erythematosus. *J. Rheumatol.* 24(5), 871–878 (1997).

27. Ludivico CL, Zweiman B, Myers AR, Hebert J, Green PA: Predictive value of anti-DNA antibody and selected laboratory studies in systemic lupus erythematosus. *J. Rheumatol.* 7(6), 843–849 (1980).
28. Raz E, Brezis M, Rosenmann E, Eilat D: Anti-DNA antibodies bind directly to renal antigens and induce kidney dysfunction in the isolated perfused rat kidney. *J. Immunol.* 142(9), 3076–3082 (1989).
29. Duchosal MA, McConahey PJ, Robinson CA, Dixon FJ: Transfer of human systemic lupus erythematosus in severe combined immunodeficient (SCID) mice. *J. Exp. Med.* 172(3), 985–988 (1990).
30. Ashany D, Hines J, Gharavi A, Mouradian J, Elkon KB: Analysis of autoantibody production in SCID-systemic lupus erythematosus (SLE) chimeras. *Clin. Exp. Immunol.* 88(1), 84–90 (1992).
31. Campion EW: Desperate diseases and plasmapheresis. *N. Engl. J. Med.* 326(21), 1425–1427 (1992).
32. Lewis EJ, Hunsicker LG, Lan SP, Rohde RD, Lachin JM: A controlled trial of plasmapheresis therapy in severe lupus nephritis. The Lupus Nephritis Collaborative Study Group. *N. Engl. J. Med.* 326(21), 1373–1379 (1992).
33. Ng KP, Cambridge G, Leandro MJ, Edwards JC, Ehrenstein M, Isenberg DA: B cell depletion therapy in systemic lupus erythematosus: long term follow up and predictors of response. *Ann. Rheum. Dis.* 66(9), 1259–1262 (2007).
34. Leandro MJ, Cambridge G, Edwards JC, Ehrenstein MR, Isenberg DA: B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. *Rheumatology (Oxford)* 44(12), 1542–1545 (2005).
35. Anolik JH: Anti-B-cell therapy: targetting B-cells in SLE. Presented at: *EULAR*. Barcelona, Spain, June 13–16 (Abstract SP0033) (2007).
36. van Venrooij WJ, Vossenaar ER, Zendman AJ: Anti-CCP antibodies: the new rheumatoid factor in the serology of rheumatoid arthritis. *Autoimmun. Rev.* 3(Suppl. 1), S17–S19 (2004).
37. Vossenaar ER, van Venrooij WJ: Citrullinated proteins: sparks that may ignite the fire in rheumatoid arthritis. *Arthritis. Res. Ther.* 6(3), 107–111 (2004).
38. Vossenaar ER, Despres N, Lapointe E *et al.*: Rheumatoid arthritis specific anti-Sa antibodies target citrullinated vimentin. *Arthritis. Res. Ther.* 6(2), R142–R150 (2004).
39. Vossenaar ER, Smeets TJ, Kraan MC, Raats JM, van Venrooij WJ, Tak PP: The presence of citrullinated proteins is not specific for rheumatoid synovial tissue. *Arthritis Rheum.* 50(11), 3485–3494 (2004).
40. Baeten D, Kruithof E, De Rycke L *et al.*: Diagnostic classification of spondylarthropathy and rheumatoid arthritis by synovial histopathology: a prospective study in 154 consecutive patients. *Arthritis Rheum.* 50(9), 2931–2941 (2004).

•• **Demonstrates that plasma cell infiltration in synovium is specific for RA.**

41. Masson-Bessiere C, Sebbag M, Durieux JJ *et al.*: In the rheumatoid pannus, anti-filaggrin autoantibodies are produced by local plasma cells and constitute a higher proportion of IgG than in synovial fluid and serum. *Clin. Exp. Immunol.* 119(3), 544–552 (2000).
42. Iwaki-Egawa S, Matsuno H, Ogawa Y, Watanabe Y: Production of anti-CCP antibodies and matrix metalloproteinase-3 by human rheumatoid arthritis synovial tissues using SCID mice. *Ann. Rheum. Dis.* 64(7), 1094–1095 (2005).
43. Rodriguez-Bayona B, Perez-Venegas JJ, Rodriguez C, Brieva JA: CD95-mediated control of anti-citrullinated protein/peptides antibodies (ACPA)-producing plasma cells occurring in rheumatoid arthritis inflamed joints. *Rheumatology (Oxford)* 46(4), 612–616 (2007).
44. Reparon-Schuijt CC, van Esch WJ, van Kooten C *et al.*: Secretion of anti-citrulline-containing peptide antibody by B lymphocytes in rheumatoid arthritis. *Arthritis Rheum.* 44(1), 41–47 (2001).
45. Caspi D, Anouk M, Golan I *et al.*: Synovial fluid levels of anti-cyclic citrullinated peptide antibodies and IgA rheumatoid factor in rheumatoid arthritis, psoriatic arthritis, and osteoarthritis. *Arthritis Rheum.* 55(1), 53–56 (2006).
46. van der Helm-van Mil AH, Verpoort KN, Breedveld FC, Toes RE, Huizinga TW: Antibodies to citrullinated proteins and differences in clinical progression of rheumatoid arthritis. *Arthritis. Res. Ther.* 7(5), R949–R958 (2005).
47. Ronnelid J, Wick MC, Lampa J *et al.*: Longitudinal analysis of citrullinated protein/peptide antibodies (anti-CP) during 5 year follow up in early rheumatoid arthritis: anti-CP status predicts worse disease activity and greater radiological progression. *Ann. Rheum. Dis.* 64(12), 1744–1749 (2005).
48. Del Val DA, Ibanez BR, Fito MC, Gutierrez PR, Loza CE: Anti-cyclic citrullinated peptide antibody in rheumatoid arthritis: Relation with disease aggressiveness. *Clin. Exp. Rheumatol.* 24(3), 281–286 (2006).
49. Machold KP, Stamm TA, Nell VP *et al.*: Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. *Rheumatology (Oxford)* 46(2), 342–349 (2007).
50. Glasnovic M, Bosnjak I, Vcev A *et al.*: Anti-citrullinated antibodies, radiological joint damages and their correlations with disease activity score (DAS28). *Coll. Antropol.* 31(1), 345–348 (2007).
51. Greiner A, Plischke H, Kellner H, Gruber R: Association of anti-cyclic citrullinated peptide antibodies, anti-citrullin antibodies, and IgM and IgA rheumatoid factors with serological parameters of disease activity in rheumatoid arthritis. *Ann. NY Acad. Sci.* 1050, 295–303 (2005).
52. Nielen MM, van Schaardenburg D, Reesink HW *et al.*: Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum.* 50(2), 380–386 (2004).
53. Rantapaa-Dahlqvist S, de Jong BA, Berglin E *et al.*: Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum.* 48(10), 2741–2749 (2003).
54. Kuhn KA, Kulik L, Tomooka B *et al.*: Antibodies against citrullinated proteins enhance tissue injury in experimental autoimmune arthritis. *J. Clin. Invest.* 116(4), 961–973 (2006).
55. Edwards JC, Szczepanski L, Szechinski J *et al.*: Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N. Engl. J. Med.* 350(25), 2572–2581 (2004).
56. Cohen SB, Emery P, Greenwald MW *et al.*: Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum.* 54(9), 2793–2806 (2006).

57. Emery P, Fleischmann R, Filipowicz-Sosnowska A *et al.*: The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum.* 54(5), 1390–1400 (2006).
58. Cambridge G, Leandro MJ, Edwards JC *et al.*: Serologic changes following B lymphocyte depletion therapy for rheumatoid arthritis. *Arthritis Rheum.* 48(8), 2146–2154 (2003).
59. Teng YK, Levarht EW, Hashemi M *et al.*: B-cell activity in synovium predicts responsiveness to rituximab in patients with refractory rheumatoid arthritis. *Arthritis Rheum.* (In Press) (2007).
60. Kavanaugh A, Rosengren S, Lee SJ *et al.*: Assessment of rituximab's immunomodulatory synovial effects (the ARISE trial). I: clinical and synovial biomarker results. *Ann. Rheum. Dis.* (Epub ahead of print) (2007).
61. Alessandri C, Bombardieri M, Papa N *et al.*: Decrease of anti-cyclic citrullinated peptide antibodies and rheumatoid factor following anti-TNFα therapy (infliximab) in rheumatoid arthritis is associated with clinical improvement. *Ann. Rheum. Dis.* 63(10), 1218–1221 (2004).
62. Bobbio-Pallavicini F, Alpini C, Caporali R, Avalle S, Bugatti S, Montecucco C: Autoantibody profile in rheumatoid arthritis during long-term infliximab treatment. *Arthritis. Res. Ther.* 6(3), R264–R272 (2004).
63. Chen HA, Lin KC, Chen CH *et al.*: The effect of etanercept on anti-cyclic citrullinated peptide antibodies and rheumatoid factor in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 65(1), 35–39 (2006).
64. De Rycke L, Verhelst X, Kruithof E *et al.*: Rheumatoid factor, but not anti-cyclic citrullinated peptide antibodies, is modulated by infliximab treatment in rheumatoid arthritis. *Ann. Rheum. Dis.* 64(2), 299–302 (2005).
65. Mikuls TR, O'Dell JR, Stoner JA *et al.*: Association of rheumatoid arthritis treatment response and disease duration with declines in serum levels of IgM rheumatoid factor and anti-cyclic citrullinated peptide antibody. *Arthritis Rheum.* 50(12), 3776–3782 (2004).
66. Kraan MC, Haringman JJ, Post WJ, Versendaal J, Breedveld FC, Tak PP: Immunohistological analysis of synovial tissue for differential diagnosis in early arthritis. *Rheumatology (Oxford)* 38(11), 1074–1080 (1999).
67. Iguchi T, Matsubara T, Kawai K, Hirohata K: Clinical and histologic observations of monoarthritis. Anticipation of its progression to rheumatoid arthritis. *Clin. Orthop. Relat. Res.* (250), 241–249 (1990).
68. Konttinen YT, Bergroth V, Nordstrom D *et al.*: Cellular immunohistopathology of acute, subacute, and chronic synovitis in rheumatoid arthritis. *Ann. Rheum. Dis.* 44(8), 549–555 (1985).
69. Odendahl M, Mei H, Hoyer BF *et al.*: Generation of migratory antigen-specific plasma blasts and mobilization of resident plasma cells in a secondary immune response. *Blood* 105(4), 1614–1621 (2005).
- **Postulates the theory of competition for survival niches for plasma cells to explain life-long antibody secretion.**
70. Bernasconi NL, Traggiai E, Lanzavecchia A: Maintenance of serological memory by polyclonal activation of human memory B cells. *Science* 298(5601), 2199–2202 (2002).
- **Postulates the theory of polyclonal activation of memory B cells to maintain life-long serum titers against recall antigens.**
71. van Laar JM, Melchers M, Teng YK *et al.*: Sustained secretion of immunoglobulin by long-lived human tonsil plasma cells. *Am. J. Pathol.* 171(3), 917–927 (2007).
- **Demonstrates that plasma cell survival is dependent upon its environment.**
72. Cassese G, Arce S, Hauser AE *et al.*: Plasma cell survival is mediated by synergistic effects of cytokines and adhesion-dependent signals. *J. Immunol.* 171(4), 1684–1690 (2003).
73. Nossal GJ, Makela O: Kinetic studies on the incidence of cells appearing to form two antibodies. *J. Immunol.* 88, 604–612 (1962).
74. Cyster JG: Homing of antibody secreting cells. *Immunol. Rev.* 194, 48–60 (2003).
75. Minges Wols HA, Underhill GH, Kansas GS, Witte PL: The role of bone marrow-derived stromal cells in the maintenance of plasma cell longevity. *J. Immunol.* 169(8), 4213–4221 (2002).
76. O'Connor BP, Raman VS, Erickson LD *et al.*: BCMA is essential for the survival of long-lived bone marrow plasma cells. *J. Exp. Med.* 199(1), 91–98 (2004).
77. Herman JH, Bradley J, Ziff M, Smiley JD: Response of the rheumatoid synovial membrane to exogenous immunization. *J. Clin. Invest.* 50(2), 266–273 (1971).
78. Pope RM, Pahlavani MA, LaCour E, Sambol S, Desai BV: Antigenic specificity of rheumatoid synovial fluid lymphocytes. *Arthritis Rheum.* 32(11), 1371–1380 (1989).
79. Manz RA, Arce S, Cassese G, Hauser AE, Hiepe F, Radbruch A: Humoral immunity and long-lived plasma cells. *Curr. Opin Immunol.* 14(4), 517–521 (2002).
80. Hoyer BF, Manz RA, Radbruch A, Hiepe F: Long-lived plasma cells and their contribution to autoimmunity. *Ann. NY Acad. Sci.* 1050, 124–133 (2005).
81. Rahman J, Staines NA: Contribution of the spleen, lymph nodes and bone marrow to the antibody response in collagen-induced arthritis in the rat. *Clin. Exp. Immunol.* 85(1), 48–54 (1991).
82. Shi K, Hayashida K, Kaneko M *et al.*: Lymphoid chemokine B cell-attracting chemokine-1 (CXCL13) is expressed in germinal center of ectopic lymphoid follicles within the synovium of chronic arthritis patients. *J. Immunol.* 166(1), 650–655 (2001).
83. Imai Y, Sato T, Yamakawa M, Kasajima T, Suda A, Watanabe Y: A morphological and immunohistochemical study of lymphoid germinal centers in synovial and lymph node tissues from rheumatoid arthritis patients with special reference to complement components and their receptors. *Acta Pathol. Jpn* 39(2), 127–134 (1989).
84. Randen I, Mellbye OJ, Forre O, Natvig JB: The identification of germinal centres and follicular dendritic cell networks in rheumatoid synovial tissue. *Scand. J. Immunol.* 41(5), 481–486 (1995).
85. Takemura S, Braun A, Crowson C *et al.*: Lymphoid neogenesis in rheumatoid synovitis. *J. Immunol.* 167(2), 1072–1080 (2001).
86. Jacquot S, Kobata T, Iwata S, Morimoto C, Schlossman SF: CD154/CD40 and CD70/CD27 interactions have different and sequential functions in T cell-dependent B cell responses: enhancement of plasma cell differentiation by CD27 signaling. *J. Immunol.* 159(6), 2652–2657 (1997).
87. Avery DT, Ellyard JI, Mackay F, Corcoran LM, Hodgkin PD, Tangye SG: Increased expression of CD27 on activated human memory B cells correlates with their commitment to the plasma cell lineage. *J. Immunol.* 174(7), 4034–4042 (2005).
88. Miyashita T, McIlraith MJ, Grammer AC *et al.*: Bidirectional regulation of human B cell responses by CD40-CD40 ligand interactions. *J. Immunol.* 158(10), 4620–4633 (1997).

89. Lipsky PE, Attrep JF, Grammer AC, McIlraith MJ, Nishioka Y: Analysis of CD40–CD40 ligand interactions in the regulation of human B cell function. *Ann. NY Acad. Sci.* 815, 372–383 (1997).
90. Wehrli N, Legler DF, Finke D *et al.*: Changing responsiveness to chemokines allows medullary plasmablasts to leave lymph nodes. *Eur. J. Immunol.* 31(2), 609–616 (2001).
91. Nie Y, Waite J, Brewer F, Sunshine MJ, Littman DR, Zou YR: The role of CXCR4 in maintaining peripheral B cell compartments and humoral immunity. *J. Exp. Med.* 200(9), 1145–1156 (2004).
92. Muehlinghaus G, Cigliano L, Huehn S *et al.*: Regulation of CXCR3 and CXCR4 expression during terminal differentiation of memory B cells into plasma cells. *Blood* 105(10), 3965–3971 (2005).
93. Jimenez-Boj E, Redlich K, Turk B *et al.*: Interaction between synovial inflammatory tissue and bone marrow in rheumatoid arthritis. *J. Immunol.* 175(4), 2579–2588 (2005).
•• **Demonstrates plasma cells are dominant at the junction zone of inflamed synovial tissue and periostium in RA patients.**
94. Verburg RJ, Flierman R, Sont JK *et al.*: Outcome of intensive immunosuppression and autologous stem cell transplantation in patients with severe rheumatoid arthritis is associated with the composition of synovial T cell infiltration. *Ann. Rheum. Dis.* 64(10), 1397–1405 (2005).
95. Teng YK, Verburg RJ, Verpoort KN *et al.*: Differential responsiveness to immunoablative therapy in refractory rheumatoid arthritis is associated with level and avidity of anti-cyclic citrullinated peptide autoantibodies; a case-study. *Arthritis. Res. Ther.* 9(5), R106 (2007).
96. van Oosterhout M, Levarht EW, Sont JK, Huizinga TW, Toes RE, van Laar JM: Clinical efficacy of infliximab plus methotrexate in DMARD naive and DMARD refractory rheumatoid arthritis is associated with decreased synovial expression of TNF α and IL18 but not CXCL12. *Ann. Rheum. Dis.* 64(4), 537–543 (2005).
97. Smeets TJ, Kraan MC, van Loon ME, Tak PP: Tumor necrosis factor alpha blockade reduces the synovial cell infiltrate early after initiation of treatment, but apparently not by induction of apoptosis in synovial tissue. *Arthritis Rheum.* 48(8), 2155–2162 (2003).
98. Gerlag DM, Haringman JJ, Smeets TJ *et al.*: Effects of oral prednisolone on biomarkers in synovial tissue and clinical improvement in rheumatoid arthritis. *Arthritis Rheum.* 50(12), 3783–3791 (2004).
99. Vos K, Thurlings RM, Wijbrandts CA, van Schaardenburg D, Gerlag DM, Tak PP: Early effects of rituximab on the synovial cell infiltrate in patients with rheumatoid arthritis. *Arthritis Rheum.* 56(3), 772–778 (2007).
100. Vos K, Thurlings RM, Wijbrandts CA, van Schaardenburg D, Gerlag DM, Tak PP: Dynamics of the synovial B cell response to Rituximab therapy in rheumatoid arthritis. Presented at: *EULAR.* Barcelona, Spain, June 13–16 (Abstract OP0229) (2007)
101. Tak PP, van der Lubbe PA, Cauli A *et al.*: Reduction of synovial inflammation after anti-CD4 monoclonal antibody treatment in early rheumatoid arthritis. *Arthritis Rheum.* 38(10), 1457–1465 (1995).
102. Withers DR, Fiorini C, Fischer RT, Ettinger R, Lipsky PE, Grammer AC: T cell-dependent survival of $CD20^+$ and $CD20^-$ plasma cells in human secondary lymphoid tissue. *Blood* 109(11), 4856–4864 (2007).
103. Matthes T, Werner-Favre C, Zubler RH: Cytokine expression and regulation of human plasma cells: disappearance of interleukin-10 and persistence of transforming growth factor-β 1. *Eur. J. Immunol.* 25(2), 508–512 (1995).
104. Di Girolamo N, Tedla N, Lloyd A, Wakefield D: Expression of matrix metalloproteinases by human plasma cells and B lymphocytes. *Eur. J. Immunol.* 28(6), 1773–1784 (1998).
105. Xiang Z, Cutler AJ, Brownlie RJ *et al.*: FcγRIIb controls bone marrow plasma cell persistence and apoptosis. *Nat. Immunol.* 8(4), 419–429 (2007).

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