

Autoantibodies in rheumatoid arthritis and their clinical significance

Günter Steiner and Josef Smolen

Vienna General Hospital, University of Vienna, and Ludwig Boltzmann Institute for Rheumatology, Vienna, Austria

Correspondence: Günter Steiner, PhD, Division of Rheumatology, Department of Internal Medicine III, Vienna General Hospital, Währinger Gürtel 18-20, A-1090 Vienna, Austria. Tel: +43 1 40400 4301; fax: +43 1 40400 4306; e-mail: Guenther.Steiner@akh-wien.ac.at

Received: 17 December 2001

Revisions requested: 21 December 2001

Revisions received: 13 February 2002

Accepted: 15 February 2002

Published: 26 April 2002

Arthritis Res 2002, **4** (suppl 2):S1-S5

© 2002 BioMed Central Ltd

(Print ISSN 1465-9905; Online ISSN 1465-9913)

Abstract

Autoantibodies are proven useful diagnostic tools for a variety of rheumatic and non-rheumatic autoimmune disorders. However, a highly specific marker autoantibody for rheumatoid arthritis (RA) has not yet been determined. The presence of rheumatoid factors is currently used as a marker for RA. However, rheumatoid factors have modest specificity (~70%) for the disease. In recent years, several newly characterized autoantibodies have become promising candidates as diagnostic indicators for RA. Antikeratin, anticitrullinated peptides, anti-RA33, anti-Sa, and anti-p68 autoantibodies have been shown to have >90% specificity for RA. These autoantibodies are reviewed and the potential role of the autoantibodies in the pathogenesis of RA is briefly discussed.

Keywords: autoantibodies, diagnostic factors, pathogenesis, rheumatoid arthritis

Introduction

Autoantibodies are a common and characteristic feature of rheumatic autoimmune diseases. Although the majority of autoantibodies do not seem to play a major pathogenic role in these disorders, some of them have proven extremely useful as diagnostic tools and indicators of disease activity [1]. Well-known examples of diagnostic and disease activity indicators are autoantibodies to double-stranded DNA in systemic lupus erythematosus (SLE) [2], to topoisomerase I (Scl-70) in scleroderma [3], to histidyl-tRNA synthetase (Jo-1) in poly/dermatomyositis [4], and to proteinase 3 in Wegener's granulomatosis [5].

Only a few autoantibodies are truly disease specific, however, and their prevalence, or sensitivity, in the respective disorders is usually <50%. However, antibodies that are not strictly specific are also used for diagnostic purposes. Anti-Ro antibodies, for instance, are present in

70–80% of patients with primary Sjögren's syndrome, but they also occur in approximately 50% of patients with SLE and in lower proportions (usually <10%) in other autoimmune diseases. Anti-Ro antibodies are nevertheless considered a valuable tool for the diagnosis of both Sjögren's syndrome and SLE.

The lack of a specific marker antibody is particularly true for rheumatoid arthritis (RA). Rheumatoid factors (RF), the immunologic hallmark of RA, have modest RA disease specificity (up to 66%) [6]. This has stimulated a search for novel antibodies and their respective target molecules that could be useful for the diagnosis of RA. In addition, identification of these targets might further enlighten our understanding of the pathogenesis of this disorder. Among the autoantibodies described in recent years, several are promising candidates as diagnostic indicators for RA and may soon become part of the diagnostic reper-

Table 1

Novel autoantibodies of potential diagnostic relevance in rheumatoid arthritis

Antibody (year)	Antigen (year)	Sensitivity (%)	Specificity (%)	References
Antikeratin (1979)	Filaggrin (1993)	40	92–99	[4–9]
	Anticitrullinated peptides (1998) = deiminated arginine identified in filaggrin (1999) and in fibrin (2001)	53*	96	[8,10–13]
Anti-RA33 (1989)	hnRNP-A2 (1992)	32	90–96 [†]	[6,14–21]
Anti-Sa (1994)	50 kDa protein, unidentified	42	98	[11,20,22,23]
Anti-p68 (1995)	BiP/grp78 (2001)	40	96	[24,25]

BiP, immunoglobulin binding protein; grp78, glucose-regulated protein 78 kDa; hnRNP-A2, heterogeneous nuclear ribonucleoprotein A2. * In rheumatoid factor-negative patients, approximately 15%. [†] Specificity of anti-RA33 when a diagnosis of systemic lupus erythematosus (SLE) or mixed connective tissue disease (MCTD) can be excluded, or in the absence of autoantibodies associated with SLE or MCTD (anti-DNA, anti-Sm, anti-U1 RNP, anti-Ro, anti-La).

Table 2

Detection of autoantibodies in arthritis animal models

Model	Rheumatoid factor	Anti-A2/anti-RA33	Anticitrulline
Collagen-induced arthritis	–	–	–
Pristane-induced arthritis	–	+	ND
TNF transgenic mice	–	+	–
MRL/lpr mice	+	+	ND

TNF, tumor necrosis factor; ND, not determined.

toire (Table 1) [4–25]. Interestingly, some of these autoantibodies also occur in experimental models of arthritis including tumor necrosis factor-transgenic mice, which develop a rapidly progressing arthritis closely resembling RA (Table 2) [7,10].

Autoantibodies

Rheumatoid factors

RF, autoantibodies that react with the Fc portion of IgG, have been on the rheumatologic stage for longer than 60 years and are still the only established serologic marker of RA [8]. RF can be detected in 60–80% of RA patients and are thus fairly sensitive in diagnosing RA. However, the specificity of RF as a diagnostic indicator for RA is substantially inferior to that of autoantibodies used for the diagnosis of other rheumatic autoimmune diseases. Moreover, RF occur less frequently or are of low titer in early disease stages when a clear diagnosis is often not yet possible. Apart from RA, high-titer RF are also present in the majority of patients with primary Sjögren’s syndrome and can be found in lower proportions (and usually also in lower titers) in all other rheumatic autoimmune diseases, as well as in a number of non-autoimmune conditions such as osteoarthritis or chronic infections [6,8].

The disease specificity of RF for rheumatic diseases is dependent on the concentration (titer) used as a cut-off and is considerably higher at elevated titers, albeit at the expense of sensitivity (Table 3). Furthermore, RF can be a prognostic indicator because they are related to increased severity of RA, such as the presence of erosive disease, more rapid disease progression, and worse outcome. Although RF may be involved in RA pathogenesis, their role is still not entirely clear. Interestingly, RF do not occur in experimental models of RA. Only MRL/lpr mice that suffer from lupus-like disease with anti-dsDNA and anti-Sm antibodies express RF [11]. In addition, these mice present with arthritis, which may become erosive, as well as other overlapping disease features [12].

Antikeratin, antifilaggrin, and anticitrulline antibodies

Antikeratin antibodies (AKA) were first described in 1979 [13] and have been repeatedly shown to be highly specific for RA [9,14]. The antigen targeted by AKA was identified in 1993 as the intermediate filament-aggregating protein filaggrin, which is expressed exclusively in keratinizing epithelial cells [15]. Subsequent studies showed that the AKA/antifilaggrin antibodies recognized epitopes that contained the amino acid citrulline, which is generated post-translationally from arginine by the enzyme peptidylarginine deiminase [16,17]. These antibodies are therefore now generally called anticitrullinated peptide or anticitrulline antibodies. However, these autoantibodies recognize citrulline-containing peptides, which are not necessarily derived from filaggrin. Nevertheless, the disease specificity of anticitrulline antibodies for RA is high (96%), and the reported sensitivity of RA patients for anticitrulline autoantibodies is 65%, which is comparable with that of RF. The diagnostic value of anticitrulline antibodies is further substantiated by their presence in sera from patients with early RA, although they seem to occur mainly in RF-positive sera [18,19].

Table 3**Sensitivity and specificity of rheumatoid factor**

Diagnosis	Rheumatoid factor (% positive patients)*		
	≥ 15 U/ml	≥ 50 U/ml	≥ 100 U/ml
Rheumatoid arthritis	66	46	26
Sjögren's syndrome	62	52	33
SLE	27	10	3
MCTD	23	13	6
Scleroderma	44	18	2
Polymyositis	18	0	0
Reactive arthritis	0	0	0
Osteoarthritis	25	4	4
Healthy controls	13	0	0
Sensitivity (%)	66	46	26
Specificity (%)	72	88 (92) [†]	95 (98) [†]

SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease. * Rheumatoid factor was determined by nephelometry in 100 patients with RA, in more than 200 patients with other rheumatic disease, and in 30 healthy controls. [†] Specificity when a diagnosis of Sjögren's syndrome can be excluded.

As filaggrin is an epidermal protein, it presumably does not represent the actual antigen of the anticitrulline autoimmune response, which remains to be identified. A promising candidate antigen for this autoimmune response is fibrin, which is present in the synovium of RA patients. It has recently been shown that antifilaggrin and anticitrulline antibodies recognize citrullinated fibrin [22]. It is thus conceivable that locally produced antibodies against citrullinated target structures may contribute to the inflammatory and destructive processes in the rheumatoid joint [20]. Interestingly, among experimental forms of arthritis, anticitrulline antibodies have not been observed (Table 2).

Anti-A2/anti-RA33 antibodies

Anti-A2/anti-RA33 antibodies are directed to the heterogeneous nuclear ribonucleoprotein A2 (hnRNP-A2), a nuclear protein that is involved in mRNA splicing and transport [21,23]. The antibodies occur in approximately one-third of RA patients but can also be detected in 20–30% of patients with SLE and in up to 40% of patients with the rare overlap syndrome mixed connective tissue disease (MCTD). The sensitivity of RA patients for anti-A2/anti-RA33 autoantibodies is therefore low (~40%). Nevertheless, in a representative cohort of patients with various rheumatic diseases including autoimmune and non-autoimmune arthritides, the specificity of anti-A2/anti-RA33 antibodies for RA was approximately 90% [24,25]. However, if a diagnosis of SLE and MCTD (or MCTD alone) is excluded or if there is an absence of

autoantibodies associated with SLE (such as anti-DNA, anti-Sm, and anti-U1 RNP antibodies), the specificity of anti-RA33 antibodies for RA can be as high as 96% [25].

Importantly, other arthritides such as osteoarthritis, reactive arthritis, and psoriatic arthropathy are usually anti-A2/anti-RA33 negative. Moreover, these antibodies may be present in early disease stages, particularly in RF-negative sera; although, as is true with other autoantibodies, at slightly lower frequency than in established disease [14,26]. The antigen targeted is more or less ubiquitously expressed, although expression levels may greatly differ between tissues. Recent data from our laboratory indicate that hnRNP-A2/RA33 is overexpressed in synovial membranes of RA patients, where it might form a target for autoreactive B and T cells [10]. Of particular interest, anti-A2/anti-RA33 antibodies are present in early stages of disease in MRL/lpr mice, where they precede anti-dsDNA antibody formation, and in tumor necrosis factor- α transgenic mice (which develop severe erosive arthritis similar to RA) [7,10]. These data suggest that autoimmunity against hnRNP-A2/RA33 may be involved in the pathophysiology of these models, and possibly in human disease.

Other antinuclear antibodies

Antinuclear antibodies are found in approximately 50% of RA patients. With the exception of anti-RA33 and antibodies to Epstein-Barr virus nuclear antigen, specific antinuclear antibody subsets among patients with connective tissue diseases are very rare. Anti-Ro may occasionally be present in RA patients, especially if they suffer from secondary Sjögren's syndrome. Although antibodies to double-stranded DNA are also very rare among RA patients, it is of interest that in the course of infliximab therapy both an increase (or *de novo* occurrence) of antinuclear antibodies and the development of antibodies to double-stranded DNA, particularly of the IgM type, have been observed [27,28]. Nevertheless, the presence of drug-induced lupus-like syndrome is rare (approximately 0.5% of infliximab-treated patients) and is no more common than that observed with several other disease-modifying antirheumatic drugs. Furthermore, it usually does not involve major organs [27], and is reversible upon mild therapeutic measures or cessation of therapy.

Anti-Sa antibodies

Anti-Sa antibodies are directed to a 50 kDa protein of unknown structure and function that has been isolated from human tissues (spleen, placenta, rheumatoid synovium). Anti-Sa autoantibodies are detected in approximately 40% of patients with established RA but less often in patients with early disease [29,30]. The reported specificity of anti-Sa antibodies for RA range between 92 and 98%, which compares favorably with marker antibodies for other autoimmune diseases. As suggested by Hayem *et al.* [31], who found the incidence of these antibodies to

be significantly increased in RA patients with severe destructive disease, determination of anti-Sa antibodies may be of prognostic benefit. In a recent prospective study in patients with recent onset synovitis, anti-Sa had the highest specificity and prognostic value of all autoantibodies investigated [18].

Anti-BiP antibodies

Autoantibodies to a ubiquitously expressed 68 kDa glycoprotein were described in 1995 by Blass *et al.* [32]. The target of anti-p68 antibodies was recently identified as the chaperone, or stress protein immunoglobulin heavy-chain binding protein (BiP). It is also known as glucose-regulated protein of 78 kDa (grp78), a member of the 70 kDa heat-shock protein family, and is localized in the endoplasmic reticulum [33]. Anti-BiP autoantibodies are found in the sera of more than 60% of RA patients [32]. The specificity of anti-BiP antibodies for RA has been reported as 96%, making these antibodies promising candidates for the diagnosis of RA. Furthermore, it will be important to learn whether anti-BiP antibodies develop early in the disease process. Similar to hnRNP-A2/RA33 and fibrin, BiP has been shown to be highly expressed in synovial tissue. Because it seems to form a target for autoreactive T cells of RA patients, BiP may be one of the antigens driving the pathologic autoimmune process in RA [33].

Conclusion

The search for autoantigens that might be relevant in both the pathogenesis and diagnosis of RA has led to the characterization of several interesting and novel autoantibodies that appear to be considerably more disease specific than RF. These antibodies can be found in the sera of 30–65% of RA patients, with reported specificities for RA of up to 98%.

Although their usefulness for diagnosis of RA awaits clinical confirmation, these antibodies appear to be very promising candidates for diagnostic applications. Their presence suggests that a diagnosis of RA in the absence of RF-positive sera can potentially be made. In addition, the presence of these antibodies may be regarded as confirmatory when present in conjunction with RF [14,18,30]. RF analysis should therefore be accompanied with other autoantibody assays, particularly when the RF titer is low or absent, or when the diagnosis is uncertain. Commercial enzyme-linked immunosorbent assays are currently available for antibodies to citrullinated peptides and anti-A2/anti-RA33, and assays for other autoantibodies may soon be available commercially. It will thus be interesting to determine whether these assays prove useful in clinical practice.

It is not clear to date whether these autoimmune responses play a pathogenetic role in the development of RA or are a consequence of the chronic inflammatory

process of RA, even when the autoantibodies precede the manifestation of clinical symptoms [34,35]. Considerable evidence exists for the pathogenetic involvement of RF; therefore, a potential role for autoantibodies in the disease process of RA should not be ignored. This potential role is bolstered by a novel transgenic mouse model of RA where an autoantibody directed to the ubiquitously expressed glycolytic enzyme glucose-6-phosphate isomerase was sufficient to induce erosive arthritis [36,37]. Importantly, the occurrence of such autoantibodies in sera from RA patients was reported recently [38]. Therefore, the appearance of autoantibodies may be more than diagnostically useful epiphenomena. For the next few years, it will be a challenging task to characterize novel RA-specific autoantibodies and to elucidate the role of the autoimmune response in the pathogenesis of RA.

Acknowledgement

Supported in part by the Interdisciplinary Cooperation Project of the Federal Ministry of Science

References

1. von Muhlen CA, Tan EM: **Autoantibodies in the diagnosis of systemic rheumatic disease.** *Semin Arthritis Rheum* 1995, **24**: 323-358.
2. Arbuckle MR, James JA, Kohlhase KF, Rubertone MV, Dennis GJ, Harley JB: **Development of anti-dsDNA autoantibodies prior to clinical diagnosis of systemic lupus erythematosus.** *Scand J Immunol* 2001, **54**:211-219.
3. Gussin HA, Ignat GP, Varga J, Teodorescu M: **Anti-topoisomerase I (anti-Sci-70) antibodies in patients with systemic lupus erythematosus.** *Arthritis Rheum* 2001, **44**:376-383.
4. Nishikai M, Ohya K, Kosaka M, Akiya K, Tojo T: **Anti-Jo-1 antibodies in polymyositis or dermatomyositis: evaluation by ELISA using recombinant fusion protein Jo-1 as antigen.** *Br J Rheumatol* 1998, **37**:357-361.
5. van der Geld YM, Limburg PC, Kallenberg CG: **Proteinase 3, Wegener's autoantigen: from gene to antigen.** *J Leukoc Biol* 2001, **69**:177-190.
6. Smolen JS: **Rheumatoid arthritis.** In *Manual of Biological Markers of Disease*. Edited by Maini RN, van Venrooij WJ. Amsterdam: Kluwer Academic Publishers; 1996:1-18.
7. Schett G, Hayer S, Tohidast-Akrad M, Schmid BJ, Lang S, Turk B, Kainberger F, Haralambous S, Kollias G, Newby AC, Xu Q, Steiner G, Smolen J: **Adenovirus-based overexpression of tissue inhibitor of metalloproteinases 1 reduces tissue damage in the joints of tumor necrosis factor alpha transgenic mice.** *Arthritis Rheum* 2001, **44**:2888-2898.
8. Tighe H, Carson DA: **Rheumatoid factors.** In *Textbook of Rheumatology*, 5th edn. Edited by Kelley WN, Harris ED, Ruddy S, Sledge CB. Philadelphia, PA: WB Saunders; 1997:241-249.
9. Youinou P, Serre G: **The antiperinuclear factor and antikeratin antibody systems.** *Int Arch Allergy Immunol* 1995, **107**:508-518.
10. Dumortier H, Monneaux F, Jahn-Schmid B, Briand JP, Skriner K, Cohen PL, Smolen JS, Steiner G, Muller S: **B and T cell responses to the spliceosomal heterogeneous nuclear ribonucleoproteins A2 and B1 in normal and lupus mice.** *J Immunol* 2000, **165**:2297-2305.
11. Eisenberg RA, Thor LT, Dixon FJ: **Serum-serum interactions in autoimmune mice.** *Arthritis Rheum* 1979, **22**:1074-1081.
12. Koopman WJ, Gay S: **The MRL-lpr/lpr mouse. A model for the study of rheumatoid arthritis.** *Scand J Rheumatol* 1988, **75**: 284-289.
13. Young BJ, Mallya RK, Leslie RD, Clark CJ, Hamblin TJ: **Antikeratin antibodies in rheumatoid arthritis.** *Br Med J* 1979, **14**: 97-99.
14. Cordonnier C, Meyer O, Palazzo E, de Bandt M, Elias A, Nicaise P, Haim T, Kahn MF, Chatellier G: **Diagnostic value of anti-RA33**

- antibody, antikeratin antibody, antiperinuclear factor and antinuclear antibody in early rheumatoid arthritis: comparison with rheumatoid factor. *Br J Rheumatol* 1996, **35**:620-624.
15. Simon M, Girbal E, Sebbag M, Gomes-Daudrix V, Vincent C, Salama G, Serre G: **The cytokeratin filament-aggregating protein filaggrin is the target of the so-called 'antikeratin antibodies', autoantibodies specific for rheumatoid arthritis.** *J Clin Invest* 1993, **92**:1387-1393.
 16. 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* 1998, **101**:273-281.
 17. Girbal-Neuhauser E, Durieux JJ, Arnaud M, Dalbon P, Sebbag M, Vincent C, Simon M, Senshu T, Masson Bessiere C, Jolivet Reynaud C, Jolivet M, Serre G: **The epitopes targeted by the rheumatoid arthritis-associated antifilaggrin autoantibodies are posttranslationally generated on various sites of (pro)filaggrin by deimination of arginine residues.** *J Immunol* 1999, **162**:585-594.
 18. Goldbach-Mansky R, Lee J, McCoy A, Hoxworth J, Yarburo C, Smolen JS, Steiner G, Rosen A, Zhang C, Menard HA, Zhou ZJ, Palosua T, van Venrooij WJ, Wilder RL, Klippel JH, Schumacher HR Jr, El Gabalawy HS: **Rheumatoid arthritis associated autoantibodies in patients with synovitis of recent onset.** *Arthritis Res* 2000, **2**:236-243.
 19. Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC, van Venrooij WJ: **The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide.** *Arthritis Rheum* 2000, **43**:155-163.
 20. Masson-Bessiere C, Sebbag M, Durieux JJ, Nogueira L, Vincent C, Girbal Neuhauser E, Durroux R, Cantagrel A, Serre G: **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* 2000, **119**:544-552.
 21. Hassfeld W, Steiner G, Hartmuth K, Kolar Z, Scherak O, Graninger W, Thumb N, Smolen J: **Demonstration of a new antinuclear antibody (anti-RA33) that is highly specific for rheumatoid arthritis.** *Arthritis Rheum* 1989, **32**:1515-1520.
 22. Masson-Bessiere C, Sebbag M, Girbal-Neuhauser E, Nogueira L, Vincent C, Senshu T, Serre G: **The major synovial targets of the rheumatoid arthritis-specific antifilaggrin autoantibodies are deiminated forms of the alpha- and beta-chains of fibrin.** *J Immunol* 2001, **166**:4177-4184.
 23. Steiner G, Hartmuth K, Skriner K, Maurer-Fogy I, Sinski A, Thalmann E, Hassfeld W, Barta A, Smolen JS: **Purification and partial sequencing of the nuclear autoantigen RA33 shows that it is indistinguishable from the A2 protein of the heterogeneous nuclear ribonucleoprotein complex.** *J Clin Invest* 1992, **90**:1061-1066.
 24. Meyer O, Tauxe F, Fabregas D, Gabay C, Goycochea M, Haim T, Elias A, Kahn MF: **Anti-RA 33 antinuclear autoantibody in rheumatoid arthritis and mixed connective tissue disease: comparison with antikeratin and antiperinuclear antibodies.** *Clin Exp Rheumatol* 1993, **11**:473-478.
 25. Hassfeld W, Steiner G, Studnicka-Benke A, Skriner K, Graninger W, Fischer I: **Autoimmune response to the spliceosome. An immunologic link between rheumatoid arthritis, mixed connective tissue disease, and systemic lupus erythematosus.** *Arthritis Rheum* 1995, **38**:777-785.
 26. Hassfeld W, Steiner G, Graninger W, Witzmann G, Schweitzer H, Smolen JS: **Autoantibody to the nuclear antigen RA33: A marker for early rheumatoid arthritis.** *Br J Rheumatol* 1993, **32**:199-203.
 27. Charles PJ, Smeenk RJ, De Jong J, Feldmann M, Maini RN: **Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials.** *Arthritis Rheum* 2000, **43**:2383-2390.
 28. Via CS, Shustov A, Rus V, Lang T, Nguyen P, Finkelman FD: **In vivo neutralization of TNF-alpha promotes humoral autoimmunity by preventing the induction of CTL.** *J Immunol* 2001, **167**:6821-6826.
 29. Despres N, Boire G, Lopez-Longo FJ, Menard HA: **The Sa system: a novel antigen-antibody system specific for rheumatoid arthritis.** *J Rheumatol* 1994, **21**:1027-1033.
 30. Hueber W, Hassfeld W, Smolen JS, Steiner G: **Sensitivity and specificity of anti-Sa autoantibodies for rheumatoid arthritis.** *Rheumatology (Oxford)* 1999, **38**:155-159.
 31. Hayem G, De Bandt M, Palazzo E, Roux S, Combe B, Eliaou JF, Sany J, Kahn MF, Meyer O: **Anti-Sa antibody is an accurate diagnostic and prognostic marker in adult rheumatoid arthritis.** *J Rheumatol* 1999, **26**:7-13.
 32. Blass S, Specker C, Lakomek HJ, Schneider EM, Schwochou M: **Novel 68 kDa autoantigen detected by rheumatoid arthritis specific antibodies.** *Ann Rheum Dis* 1995, **54**:355-360.
 33. Blass S, Union A, Raymackers J, Schumann F, Ungethüm U, Müller Steinbach S, De Keyser F, Engel JM, Burmester GR: **The stress protein BiP is over expressed and is a major B and T cell target in rheumatoid arthritis.** *Arthritis Rheum* 2001, **44**:761-771.
 34. Weyand CM, Goronzy JJ: **Pathogenesis of rheumatoid arthritis.** *Med Clin North Am* 1997, **81**:29-55.
 35. Smolen JS, Steiner G: **Are autoantibodies active players of epiphenomena?** *Curr Opin Rheumatol* 1998, **10**:201-206.
 36. Korganow AS, Ji H, Mangialaio S, Duchatelle V, Pelanda R, Martin T, Degott C, Kikutani H, Rajewsky K, Pasquali JL, Benoist C, Mathis D: **From systemic T cell self-reactivity to organ-specific autoimmune disease via immunoglobulins.** *Immunity* 1999, **10**:451-561.
 37. Matsumoto I, Staub A, Benoist C, Mathis D: **Arthritis provoked by linked T and B cell recognition of glycolytic enzyme.** *Science* 1999, **26**:1732-1735.
 38. Schaller M, Burton DR, Ditzel HJ: **Autoantibodies to GPI in rheumatoid arthritis: linkage between an animal model and human disease.** *Nat Immunol* 2001, **2**:746-753.