REVIEW ARTICLE

Neutrophil activation and B-cell stimulation in the pathogenesis of Felty's syndrome

Nishant Dwivedi[1,2], Marko Radic[1]

1 Department of Microbiology, Immunology and Biochemistry, University of Tennessee Health Sciences Center, Memphis, Tennessee, United States
2 The Immune Disease Institute and Program in Molecular and Cellular Medicine, Children's Hospital and Harvard Medical School, Boston, Massachusetts, United States

KEY WORDS

autoantibodies, histone deimination, neutrophils, NETosis, systemic uatoimmunity

ABSTRACT

Felty's syndrome (FS) is a severe arthritic disorder that features chronic neutrophil activation and progresses to neutropenia and susceptibility to unabated infections. The life-threatening manifestations of FS have focused the attention of clinical experimenters who have made persistent efforts to find new and effective therapies. This review highlights important milestones in the research on FS and draws attention to recent studies on the antigen specificity of antibodies present in patients' sera. Recent data have indicated that immunoglobulins G (IgGs) in patients with FS bind selectively and specifically to deiminated histones and neutrophil extracellular chromatin traps (NETs). Deimination is the conversion of certain arginine residues in proteins to citrullines by the enzyme peptidylarginine deiminase 4. Earlier observations had indicated that IgGs in FS patients avidly bind to citrullinated peptides. These observations suggest that NETosis, the type of cell death that is defined by the release of NETs, provides autoantigens that stimulate B cell responses in this patient group. This insight parallels recent observations in other autoimmune conditions and lends support to the paradigm that NETosis plays a leading role in the pathogenesis of antiself immune responses.

INTRODUCTION The pathogenesis of Felty's syndrome (FS) is complex. To treat and manage patients with FS, a better understanding of the disease is needed. An important first step in understanding autoimmune disease in general is to identify relevant self-antigen(s). Certain autoantibodies have diagnostic importance: anti-DNA and anticyclic citrullinated peptide enzyme-linked immunosorbent assays (ELISA) are important tests to diagnose systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), respectively. Studies of autoantibodies also reveal the mechanism involved in the expression of autoantigens and their interaction with the immune system. Genetic analysis of autoantibodies has revealed that junctional diversity and somatic mutations make essential contribution to the recognition of autoantigens.[1] Affinity maturation of antiself B-cell receptors together with clonal expansion of B cells bearing such receptors is similar to that seen against foreign antigens.[2] These studies have allowed a significant progress in identifying the autoimmune pathogenesis of some diseases. For SLE, RA, and FS, the role of autoantibodies in the disease process is not entirely clear, yet a plethora of associated self-specificities provide clues about the disease process. Because FS is characterized by the inflammation-driven, progressive destruction of neutrophils, we hypothesized that autoantigens generated during neutrophil activation might play a role in this disorder. In this review, we summarize studies that have contributed to our present knowledge of FS and discuss different mechanisms that have been proposed to explain its pathogenesis.

Felty's syndrome: an "extreme" rheumatoid disease

In 1924, Dr. A.R. Felty reported 5 patients with chronic arthritis, splenomegaly, and leucopenia, thus defining a syndrome that bears his name.[3] FS is estimated to occur in about 1% to 3% of RA patients after an average of 10 to 15 years of arthritis.[4-6] FS differs from RA by more severe arthritis and extra-articular manifestations.[4,7,8] Serologically, FS exhibits higher titers of rheumatoid factor (RF),[4,7-9] antinuclear antibodies,[7,10] and antihistone antibodies.[11] The characteristic autoimmune response, coupled with neutropenia, crippling

Correspondence to:
Marko Radic, Associate Professor, Microbiology, Immunology and Biochemistry, University of Tennessee Health Science Center, 858 Madison Avenue, Memphis, TN 38163, USA,
phone: +1-901-448-8219,
fax: +1-901-448-8462,
e-mail: mradic@uthsc.edu
Received: June 19, 2012.
Accepted: June 20, 2012.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2012; 122 (7-8): 374-379

arthritis, and frequent infections, prompted Sienknecht et al.[9] to refer to FS as a "super rheumatoid" disease. Intriguingly, FS combines features of RA and SLE and displays typical clinical findings,[7,8] supporting the notion that different pathogenic mechanisms may contribute to RA and FS pathogenesis.[12]

The most critical manifestation of FS is neutropenia, resulting in a higher incidence of bacterial infection when neutrophil counts drop below 0.5×10^9/l.[7,13] In addition, the neutrophils from FS patients are deficient in bacterial phagocytosis due to decreased expression of Fc receptors.[14] Other factors that contribute to a higher incidence of infection in FS patients include hypocomplementemia, elevated levels of circulating immune complexes,[15] impaired chemotaxis, and decreased superoxide production.[16] In conjunction with neutropenia, FS patients may also present with anemia and thrombocytopenia.[4,7]

Large granular lymphocytic leukemia: a close relative of Felty's syndrome Most patients with large granular lymphocyte (LGL) leukemia exhibit a constellation of symptoms including fatigue, fever, weight loss, and night sweats, characteristic of leukemic disorders, but they also present with arthritis, neutropenia, and splenomegaly.[17,18] The peripheral expansion of lymphocyte populations in LGL leukemia, in particular those that are derived from $CD3^+$ $CD8^+$ $CD57^+$ T cells, occurs in about 30% to 40% of FS patients.[19,20] Moreover, about 20% to 30% of patients with T-LGL expansion have RA.[21,22] Because of the shared clinical features, it has been proposed that FS and T-LGL leukemia represent 2 diseases at the opposite ends of a clinical spectrum reflecting a common mechanism.[18,23] In support of this argument, it was found that patients with FS and LGL leukemia with arthritis also share a strong association with class-II alleles, in particular with HLA-DRB1*0401.[24,25] Interestingly, no such association was found in patients with LGL leukemia without arthritis,[24,25] suggesting that at least 1 subset of the LGL syndrome is unrelated to FS. Furthermore, arthritis and extra-articular manifestations are usually more severe in FS than in LGL leukemia with arthritis.[26] Notably, hepatomegaly of FS is characterized with nodular regenerative hyperplasia, portal fibrosis, and sinusoidal lymphocytosis indicative of underlying FS vasculopathy,[27] whereas in LGL only mild sinusoidal cytotoxic T-lymphocyte (CTL) infiltration without hepatocyte necrosis is found.[28] Each of these observations suggests that the pathogenic mechanisms of FS and T-LGL leukemia may be parallel but not mechanistically identical.

Neutropenia in FS is thought to arise from a survival defect of mature neutrophils in the periphery, which induces a compensatory myeloid hyperplasia in the bone marrow and an increase of immature granulocytes in the circulation.[23] In contrast, neutropenia in LGL leukemia without RA is thought to reflect impaired proliferation of neutrophils in the bone marrow, because the accumulating LGL cells may displace other cells in the bone marrow and thus directly inhibit the proliferation and differentiation of granulocyte precursors.[23,29] Initially, investigators believed that FS and LGL leukemia could be distinguished by determining the clonality of lymphocytes: clonally restricted lymphocytes were assumed to be a characteristic of LGL leukemia, whereas a clonally diverse T-cell pool would be more indicative of FS.[30] Subsequent studies found clonal expansion in patients with FS,[20] as is often the case in autoimmune diseases. On the other hand, the expansion of lymphocytes in LGL leukemia is not always restricted to a single clone, although, as disease progresses, 1 clone usually predominates.[31] Activation of multiple T-cell clones by a chronic viral infection or an endogenous autoantigen may drive T-LGL clonal expansion.[32] The recent finding of "clonal drift" in LGL patients supports the view that a dysregulation of the CTL repertoire homeostasis, along with a sustained immunologic stimulus, rather than a genetic defect, underlies the expansion of T-LGL leukemia cells.[33]

Neutropenia in Felty's syndrome Recurrent infections due to neutropenia are the major challenge in treating FS patients.[7,13] Therefore, an understanding of the causes of neutropenia and their relationship to the overall clinical picture of FS is important. Both cellular and humoral mechanisms are thought to contribute to FS neutropenia. About 77% of FS patients have antineutrophil cytoplasmic antibodies (ANCA) that do not match other typical ANCA specificities.[34] A part of ANCA reactivity may be due to immune complexes of RF autoantibodies,[35] as it was found that RF immune complexes have the ability to activate neutrophils. Due to the biophysical properties of the immune complexes, stronger activation was induced by precipitated rather than by soluble immune complexes or noncomplexed immunoglobulin G (IgG).[36] Earlier studies also suggested that immune complexes have the potential to induce apoptosis of neutrophils, an effect that was dependent on reactive oxygen species, particularly hydrogen peroxide.[37] Autoantibodies against the eukaryotic elongation factor-1A-1 that is expressed in myeloid cell precursors are present in about 66% of FS patients but not in control individuals,[38] suggesting a possible role of autoantibodies in directly inhibiting granulopoiesis or enhancing the clearance of neutrophils. Thus, it is possible that an autoimmune process which leads to the production of RF autoantibodies, or other autoantibodies that activate neutrophils, over time contributes to FS neutropenia as a consequence of immune complex-driven neutrophil depletion.

An inherent tendency of FS sera for the activation of neutrophils is consistent with the increased activation and endothelium adherence of normal donor neutrophils that were incubated with FS sera.[36,39] Similarly, mice infused with

the sera or isolated immune complexes from FS patients, showed an immediate drop of neutrophil counts, perhaps due to the sequestration of neutrophils in the spleen following their enhanced activation and increased adherence to the endothelium.[40] Thus, the spleen may be an important organ that, following neutrophil activation in the periphery, performs multiple FS-specific roles, including neutrophil sequestration and autoantibody induction and selection. Accordingly, the splenic red pulp of FS patients expands, the sinus proliferates, macrophages infiltrate, and germinal centers develop.[41] The role of the spleen in FS pathogenesis can also be judged from the fact that nearly 100% of the patients with FS show an improvement in their neutrophil counts within 48 hours following splenectomy.[42] Yet, the lack of long-term benefits of splenectory, the inconsistent correlation between splenomegaly and neutropenia, and the common clinical features and outcomes between FS and RA patients with neutropenia but without splenomegaly led to calls for dropping splenomegaly as a required criterion for diagnosing FS.[6,20,23,25]

Neutrophil activation: at the center of Felty's syndrome pathogenesis The predominance of neutropenia in FS patients clearly points toward a connection between increased neutrophil cell death and arthritis. It remains to be established how decreased numbers of neutrophils stimulate an autoimmune response leading to arthritis. Neutropenia was proposed to be a consequence of splenic sequestration, but no evidence for neutrophil phagocytosis in the spleen of 27 FS patients could be obtained.[43] Recently, a new form of neutrophil death, NETosis, has been discovered.[44] It is possible that NETosis will provide some useful insights into the pathogenesis of FS. The process of NETosis receives its name from the formation of neutrophil extracellular traps (NETs), the release of nuclear chromatin from neutrophils following stimulation by inflammatory or infectious stimuli.[44] The release of chromatin depends on reactive oxygen species[45] and utilizes actin and microtubular filaments for extracellular deployment.[46] NETs can be induced by many bacteria, fungi, or exogenous inflammatory stimuli. Recently, lupus autoantibody complexes were found capable of inducing NETs and promoting lupus development by stimulating interferon-α production.[47] NETosis may represent a mechanism that is chronically hyperactivated in FS. If so, the rupture of neutrophils and their discharge of cellular and nuclear contents may explain why FS patients' spleens lack evidence of intact neutrophil accumulation but show all hallmarks of increased germinal center activity.[41,43]

One aspect of NETosis may help unravel the role of neutrophil activation in FS neutropenia. This is the fact that neutrophils exposed to inflammatory stimuli activate peptidylarginine deiminase IV (PAD4), leading to the deimination of arginine residues to citrullines.[48] Deimination of histones plays an important role in decondensation of chromatin during NET formation[49] and identification of deiminated histones in circulation is proposed as a marker of neutrophil activation, as may occur in sepsis.[50] Deimination of proteins is also implicated in breaking of tolerance and promoting autoimmunity, particularly in RA. Antibodies to deiminated filaggrin, previously known as antikeratin antibodies, are strongly associated with RA.[51] Several other deiminated proteins, including fibrin, vimentin, and collagen are recognized by autoantibodies in RA patients, and they have been identified in the synovial joints of RA patients.[52,53] The relationship between RA and autoantibodies to deiminated proteins is so strong that detection of antideiminated protein antibodies forms the basis of a highly sensitive and specific RA diagnostic test.[54,55] Detection of antibodies to deiminated proteins in RA patients precedes the onset of disease manifestation and their presence predicts severe erosive arthritis.[56,57] All these observations point to an important pathophysiological role for deimination in the etiology of RA. Consistent with this, it was found that PAD4 mRNA is 4- to 5-fold more stable in RA-susceptible haplotypes than in nonsusceptible haplotypes.[58]

Felty's syndrome: new insights and unanswered questions Because FS is associated with an inflammation-driven, progressive destruction of neutrophils, and deiminated histones are quite clearly the most abundant PAD4 substrates in neutrophils exposed to inflammatory stimuli, we hypothesized that FS autoantibodies would specifically bind to deiminated histones. Thus, we tested the idea by preparing deiminated histones in vitro and assaying FS sera for autoantibodies to deiminated histones. Indeed, we found that a majority of FS sera bind deiminated histones with preference over nondeiminated histones in ELISA.[59] In contrast, such a preference was rare in the sera of patients with RA and SLE. On western blots, we could identify the target of FS IgG antibodies as deiminated histone H3, although binding to deiminated core histones H2A and H4 and to linker histone H1 was also observed.[59]

The identification of autoantibodies to deiminated histones in FS suggests that neutrophil activation provides autoantigens that drive the immune response in this disorder. Because autoantibodies to deiminated histones are rare in RA, we concluded that they represent a population of autoantibodies that may serve to distinguish FS from RA. Moreover, it is tempting to conclude that such autoantibodies identify FS-specific immune activation mechanisms. If so, then autoantibodies to deiminated histones could serve a useful purpose in identifying and monitoring progression of FS. In addition, these results implicate NETosis in the immune stimulation of B cells in FS. How and when tolerance to deiminated histones is compromised are yet to be investigated, though our studies clearly suggest a role

for inflammation-induced neutrophil activation and NETs in FS pathogenesis.

Our results further suggest that tolerance of deiminated histones is compromised only after a prolonged period of immune stimulation. It is not surprising that tolerance of deiminated histones is difficult to overcome as deiminated histones form an integral part of NETs, an innate neutrophil defense mechanism against invading pathogens. Clearly, a breach in tolerance of deiminated histones may have severe consequences, as implied by a comparison between RA and FS.

We also tested sera from patients with Wegener's granulomatosis, Churg-Strauss syndrome, and patients with microscopic polyangiitis, group of vasculitis disorders characterized by the presence of ANCA, known to activate neutrophils.[60] Notably, all 3 groups of ANCA vasculitis sera showed little-to-no binding to histones. When histone binding was observed, the preference was invariably towards nondeiminated histones rather than deiminated histones.[59]

NETs are increasingly implicated in SLE pathogenesis[47,61] and, as discussed above, they may be equally important in FS. When autoantibodies to deiminated histones from FS patients were incubated with neutrophils from nonautoimmune individuals, neutrophils were activated and deimination of histones was observed.[59] Thus, FS sera contain substances that strongly activate mature neutrophils, induce histone deimination and NETosis, thus generating an abundant and continuous supply of autoantigens. It remains to be tested whether the "netting" neutrophils are cleared by the spleen where they may further stimulate autoreactive B cells. In turn, the ANCA that are secreted likely activate any newly produced neutrophils and cause a repetitive succession of neutrophil depletion and B-cell stimulation. In this way, a self-sustaining cycle of immune stimulation may evolve and give rise to FS.

Acknowledgements The authors acknowledge the research support of the Lupus Research Institute of New York and the Dana Foundation Program in Human Immunology.

REFERENCES

1 Shlomchik M, Mascelli M, Shan H, et al. Anti-DNA antibodies from autoimmune mice arise by clonal expansion and somatic mutation. J Exp Med. 1990; 171: 265-292.

2 Radic MZ, Weigert M. Genetic and structural evidence for antigen selection of anti-DNA antibodies. Annu Rev Immunol. 1994; 12: 487-520.

3 Felty AR. Chronic arthritis in the adult, associated with splenomegaly and leucopenia. A report of 5 cases of an unusual clinical syndrome. Bulletin of the Johns Hopkins Hospital, Baltimore. 1924; 35: 16.

4 Barnes CG, Turnbull AL, Vernon-Roberts B. Felty's syndrome. A clinical and pathological survey of 21 patients and their response to treatment. Ann Rheum Dis. 1971; 30: 359-374.

5 Sibley JT, Haga M, Visram DA, Mitchell DM. The clinical course of Felty's syndrome compared to matched controls. J Rheumatol. 1991; 18: 1163-1167.

6 Balint GP, Balint PV. Felty's syndrome. Best Pract Res Clin Rheumatol. 2004; 18: 631-645.

7 Campion G, Maddison PJ, Goulding N, et al. The Felty syndrome: a case-matched study of clinical manifestations and outcome, serologic features, and immunogenetic associations. Medicine (Baltimore). 1990; 69: 69-80.

8 Ruderman M, Miller LM, Pinals RS. Clinical and serologic observations on 27 patients with Felty's syndrome. Arthritis Rheum. 1968; 11: 377-384.

9 Sienknecht CW, Urowitz MB, Pruzanski W, Stein HB. Felty's syndrome. Clinical and serological analysis of 34 cases. Ann Rheum Dis. 1977; 36: 500-507.

10 Goldberg J, Pinals RS. Felty syndrome. Semin Arthritis Rheum. 1980; 10: 52-65.

11 Cohen MG, Webb J. Antihistone antibodies in rheumatoid arthritis and Felty's syndrome. Arthritis Rheum. 1989; 32: 1319-1324.

12 Scott DL, Grindulis KA, Struthers GR, et al. Progression of radiological changes in rheumatoid arthritis. Ann Rheum Dis. 1984; 43: 8-17.

13 Breedveld FC, Fibbe WE, Cats A. Neutropenia and infections in Felty's syndrome. Br J Rheumatol. 1988; 27: 191-197.

14 Breedveld FC, van den Barselaar MT, Leigh PC, et al. Phagocytosis and intracellular killing by polymorphonuclear cells from patients with rheumatoid arthritis and Felty's syndrome. Arthritis Rheum. 1985; 28: 395-404.

15 Breedveld FC, Fibbe WE, Hermans J, et al. Factors influencing the incidence of infections in Felty's syndrome. Arch Intern Med. 1987; 147: 915-920.

16 Friman C, Davis P, Starkebaum G, et al. Suppression of superoxide generation by normal polymorphonuclear leukocytes preincubated in plasma from patients with Felty's syndrome. Scand J Rheumatol. 1987; 16: 113-120.

17 Dhodapkar MV, Li CY, Lust JA, et al. Clinical spectrum of clonal proliferations of T-large granular lymphocytes: a T-cell clonopathy of undetermined significance? Blood. 1994; 84: 1620-1627.

18 Liu X, Loughran TP Jr. The spectrum of large granular lymphocyte leukemia and Felty's syndrome. Curr Opin Hematol. 2011; 18: 254-259.

19 Saway PA, Prasthofer EF, Barton JC. Prevalence of granular lymphocyte proliferation in patients with rheumatoid arthritis and neutropenia. Am J Med. 1989; 86: 303-307.

20 Bowman SJ, Bhavnani M, Geddes GC, et al. Large granular lymphocyte expansions in patients with Felty's syndrome: analysis using anti-T cell receptor V beta-specific monoclonal antibodies. Clin Exp Immunol. 1995; 101: 18-24.

21 Lamy T, Loughran TP. Large Granular Lymphocyte Leukemia. Cancer Control. 1998; 5: 25-33.

22 Loughran TP Jr. Clonal diseases of large granular lymphocytes. Blood. 1993; 82: 1-14.

23 Burks EJ, Loughran TP Jr. Pathogenesis of neutropenia in large granular lymphocyte leukemia and Felty syndrome. Blood Rev. 2006; 20: 245-266.

24 Coakley G, Brooks D, Iqbal M, et al. Major histocompatility complex haplotypic associations in Felty's syndrome and large granular lymphocyte syndrome are secondary to allelic association with HLA-DRB1 *0401. Rheumatology (Oxford). 2000; 39: 393-398.

25 Bowman SJ, Sivakumaran M, Snowden N, et al. The large granular lymphocyte syndrome with rheumatoid arthritis. Immunogenetic evidence for a broader definition of Felty's syndrome. Arthritis Rheum. 1994; 37: 1326-1330.

26 Rosenstein ED, Kramer N. Felty's and pseudo-Felty's syndromes. Semin Arthritis Rheum. 1991; 21: 129-142.

27 Thorne C, Urowitz MB, Wanless I, et al. Liver disease in Felty's syndrome. Am J Med. 1982; 73: 35-40.

28 Agnarsson BA, Loughran TP Jr, Starkebaum G, Kadin ME. The pathology of large granular lymphocyte leukemia. Hum Pathol. 1989; 20: 643-651.

29 Morice WG, Kurtin PJ, Tefferi A, Hanson CA. Distinct bone marrow findings in T-cell granular lymphocytic leukemia revealed by paraffin section immunoperoxidase stains for CD8, TIA-1, and granzyme B. Blood. 2002; 99: 268-274.

30 O'Keefe CL, Plasilova M, Wlodarski M, et al. Molecular analysis of TCR clonotypes in LGL: a clonal model for polyclonal responses. J Immunol. 2004; 172: 1960-1969.

31 Wlodarski MW, Schade AE, Maciejewski JP. T-large granular lymphocyte leukemia: current molecular concepts. Hematology. 2006; 11: 245-256.

32 Epling-Burnette PK, Loughran TP Jr. Survival signals in leukemic large granular lymphocytes. Semin Hematol. 2003; 40: 213-220.

33 Clemente MJ, Wlodarski MW, Makishima H, et al. Clonal drift demonstrates unexpected dynamics of the T-cell repertoire in T-large granular lymphocyte leukemia. Blood. 2011; 118: 4384-4393.

34 Coremans IE, Hagen EC, van der Voort EA, et al. Autoantibodies to neutrophil cytoplasmic enzymes in Felty's syndrome. Clin Exp Rheumatol. 1993; 11: 255-262.

35 Starkebaum G, Arend WP, Nardella FA, Gavin SE. Characterization of immune complexes and immunoglobulin G antibodies reactive with neutrophils in the sera of patients with Felty's syndrome. J Lab Clin Med. 1980; 96: 238-251.

36 Starkebaum G, Stevens DL, Henry C, Gavin SE. Stimulation of human neutrophil chemiluminescence by soluble immune complexes and antibodies to neutrophils. J Lab Clin Med. 1981; 98: 280-291.

37 Gamberale R, Giordano M, Trevani AS, et al. Modulation of human neutrophil apoptosis by immune complexes. J Immunol. 1998; 161: 3666-3674.

38 Ditzel HJ, Masaki Y, Nielsen H, et al. Cloning and expression of a novel human antibody-antigen pair associated with Felty's syndrome. Proc Natl Acad Sci U S A. 2000; 97: 9234-9239.

39 Hashimoto Y, Ziff M, Hurd ER. Increased endothelial cell adherence, aggregation, and superoxide generation by neutrophils incubated in systemic lupus erythematosus and Felty's syndrome sera. Arthritis Rheum. 1982; 25: 1409-1418.

40 Breedveld FC, Lafeber GJ, de Vries E, et al. Immune complexes and the pathogenesis of neutropenia in Felty's syndrome. Ann Rheum Dis. 1986; 45: 696-702.

41 van Krieken JH, Breedveld FC, te Velde J. The spleen in Felty's syndrome: a histological, mophometrical, and immunohistochemical study. Eur J Haematol. 1988; 40: 58-64.

42 Rashba EJ, Rowe JM, Packman CH. Treatment of the neutropenia of Felty syndrome. Blood Rev. 1996; 10: 177-184.

43 Laszlo J, Jones R, Silberman HR, Banks PM. Splenectomy for Felty's syndrome. Clinicopathological study of 27 patients. Arch Intern Med. 1978; 138: 597-602.

44 Brinkmann V, Reichard U, Goosmann C, et al. Neutrophil extracellular traps kill bacteria. Science. 2004; 303: 1532-1535.

45 Fuchs TA, Abed U, Goosmann C, et al. Novel cell death program leads to neutrophil extracellular traps. J Cell Biol. 2007; 176: 231-241.

46 Neeli I, Dwivedi N, Khan S, Radic M. Regulation of extracellular chromatin release from neutrophils. J Innate Immun. 2009; 1: 194-201.

47 Garcia-Romo GS, Caielli S, Vega B, et al. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. Sci Transl Med. 2011; 3: 73ra20.

48 Neeli I, Khan SN, Radic M. Histone deimination as a response to inflammatory stimuli in neutrophils. J Immunol. 2008; 180: 1895-902.

49 Wang Y, Li M, Stadler S, et al. Histone hypercitrullination mediates chromatin decondensation and neutrophil extracellular trap formation. J Cell Biol. 2009; 184: 205-213.

50 Li Y, Liu B, Fukudome EY, et al. Identification of citrullinated histone H3 as a potential serum protein biomarker in a lethal model of lipopolysaccharide-induced shock. Surgery. 2011; 150: 442-451.

51 Girbal-Neuhauser E, Durieux JJ, Arnaud M, et al. The epitopes targeted by the rheumatoid arthritis-associated antifilaggrin autoantibodies are post-translationally generated on various sites of (pro)filaggrin by deimination of arginine residues. J Immunol. 1999; 162: 585-594.

52 Van Steendam K, Tilleman K, De Ceuleneer M, et al. Citrullinated vimentin as an important antigen in immune complexes from synovial fluid of rheumatoid arthritis patients with antibodies against citrullinated proteins. Arthritis Res Ther. 2010; 12: R132.

53 Tabushi Y, Nakanishi T, Takeuchi T, et al. Detection of citrullinated proteins in synovial fluids derived from patients with rheumatoid arthritis by proteomics-based analysis. Ann Clin Biochem. 2008; 45 (Pt 4): 413-417.

54 Schellekens GA, Visser H, de Jong BA, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum. 2000; 43: 155-163.

55 van Venrooij WJ, van Beers JJ, Pruijn GJ. Anti-CCP antibodies: the past, the present and the future. Nat Rev Rheumatol. 2011; 7: 391-398.

56 Rantapää-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. 2003; 48: 2741-2749.

57 van Gaalen FA, Linn-Rasker SP, van Venrooij WJ, et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. Arthritis Rheum. 2004; 50: 709-715.

58 Suzuki A, Yamada R, Chang X, et al. Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylarginine deiminase 4, are associated with rheumatoid arthritis. Nat Genet. 2003; 34: 395-402.

59 Dwivedi N, Upadhyay J, Neeli I, et al. Felty's syndrome autoantibodies bind to deiminated histones and neutrophil extracellular chromatin traps. Arthritis Rheum. 2012; 64: 982-992.

60 Chen M, Kallenberg CG. New advances in the pathogenesis of ANCA-associated vasculitides. Clin Exp Rheumatol. 2009; 27(1 Suppl 52): S108-S114.

61 Hakkim A, Fürnrohr BG, Amann K, et al. Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. Proc Natl Acad Sci U S A. 2010; 107: 9813-9818.

Rola aktywacji neutrofili i stymulacja limfocytów B w patogenezie zespołu Felty'ego

Nishant Dwivedi[1,2], Marko Radic[1]

1 Department of Microbiology, Immunology and Biochemistry, University of Tennessee Health Sciences Center, Memphis, Tennessee, Stany Zjednoczone
2 The Immune Disease Institute and Program in Molecular and Cellular Medicine, Children's Hospital and Harvard Medical School, Boston, Massachusetts, Stany Zjednoczone

SŁOWA KLUCZOWE

autoprzeciwciała, deiminacja histonów, NET-oza, neutrofile, systemowa reakcja autoimmunologiczna

STRESZCZENIE

Zespół Felty'ego (*Felty's syndrome* – FS) jest ciężką chorobą zapalną stawów, która charakteryzuje się przewlekłą aktywacją neutrofili oraz prowadzi do neutropenii i skłonności do nieustannych zakażeń. Zagrażające życiu objawy kliniczne FS skłaniają badaczy do ciągłych poszukiwań nowych i skutecznych metod jego leczenia. W tym artykule przeglądowym omówiono przełomowe dokonania w badaniach nad FS i skoncentrowano się na wynikach ostatnio przeprowadzonych badań dotyczących swoistości antygenowej przeciwciał występujących w surowicy pacjentów z tą chorobą. Niedawno opublikowane dane wskazują, że immunoglobuliny G (IgG) pochodzące z surowicy pacjentów z FS wybiórczo i swoiście wiążą się z histonami poddanymi deiminacji i zewnątrzkomórkowymi sieciami chromatynowymi neutrofilów (*neutrophil extracellular traps* – NETs). Deiminacja jest procesem przemiany określonych reszt argininowych białek w cytrulinę za pomocą enzymu deiminazy peptydyloargininy 4. Wcześniejsze obserwacje wskazują, że IgG pacjentów z FS silnie wiążą się cytrulinowanymi peptydami. Na podstawie tych obserwacji można przypuszczać, że NET-oza, rodzaj śmierci komórki, która polega na uwolnieniu sieci NET, dostarcza antygenów, które stymulują odpowiedź limfocytów B w tej grupie pacjentów. Te spostrzeżenia pozostają w zgodzie z wynikami niedawno przeprowadzonych badań nad innymi chorobami i wspiera paradygmat, że NETоza pełni wiodącą rolę w patogenezie reakcji autoimmunologicznych.

Adres do korespondencji:
Marko Radic, Associate Professor, Microbiology, Immunology and Biochemistry, University of Tennessee Health Science Center, 858 Madison Avenue, Memphis, TN 38163, USA, phone: +1-901-448-8219, fax: +1-901-448-8462, e-mail: mradic@uthsc.edu
Praca wpłynęła: 19.06.2012.
Przyjęta do druku: 20.06.2012.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2012; 122 (7-8): 374-379