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Autoimmunity in 2014

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Abstract Our PubMed search for peer-reviewed articles published in the 2014 solar year retrieved a significantly higher number of hits compared to 2013 with a net 28 % increase. Importantly, full articles related to autoimmunity constitute approximately 5 % of immunology articles. We confirm that our understanding of autoimmunity is becoming a translational paradigm with pathogenetic elements rapidly followed by new treatment options. Furthermore, numerous clinical and pathogenetic elements and features are shared among autoimmune diseases, and this is well illustrated in the recent literature. More specifically, the past year witnessed critical revisions of our understanding and management of antiphospholipid syndrome with new exciting data on the pathogenicity of the serum anti-beta2 glycoprotein autoantibody, a better understanding of the current and new treatments for rheumatoid arthritis, and new position papers on important clinical questions such as vaccinations in patients with autoimmune disease, comorbidities, or new classification criteria. Furthermore, data confirming the important connections between innate immunity and autoimmunity via toll-like receptors or the critical role of T regulatory cells in tolerance breakdown and autoimmunity perpetuation were also reported. Lastly, genetic and epigenetic data were provided to confirm that the mosaic of autoimmunity warrants a susceptible individual background which may be geographically determined and contribute to the geoepidemiology of diseases. The 2014 literature in the autoimmunity world should be cumulatively regarded as part of an *annus mirabilis* in which, on a different level, the 2014 Annual Meeting of the American College of Rheumatology in Boston was attended by over 16,000 participants with over selected 3000 abstracts.

Keywords Tolerance breakdown · Genetics · Epigenetic · Th17 · Rheumatoid arthritis · Psoriatic arthritis · Systemic lupus erythematosus · Autoimmune liver disease

Was 2014 the *annus mirabilis* of autoimmunity?

Over the past few years [1], this manuscript has become a regular appointment in the literature to provide a quick overview of the publications dedicated to autoimmunity in the previous solar year. Indeed, each year, we witnessed a steady growth in the absolute number of articles retrieved from PubMed and calculated the ratio among publications in the significantly wider field of immunology. The case of 2014 stands out compared to previous editions as this year was associated with the steepest increase in the absolute number of publications (+28 %) (Fig. 1a) with a stable ratio with the immunology publications around 5 % (Fig. 1b). Our PubMed search performed in July 2015 retrieved 2713 articles published in English between January 1st and December 31st 2014 with 'autoimmunity' as keyword. The absolute increase is somehow surprising compared to the previous stability over the previous years (Fig. 1a). Among publications from 2014, we performed a preliminary search using the 'autoimmunity' keyword within the major journals in the areas of immunology (*Nature Immunology*, *Nature Medicine*, *Clinical and Experimental Immunology*, and *Clinical Reviews in Allergy and Immunology*) and autoimmunity (*Autoimmunity*, *Autoimmunity Reviews*, and *Journal of Autoimmunity*) and arrayed the identified articles according to major topics. We arbitrarily selected

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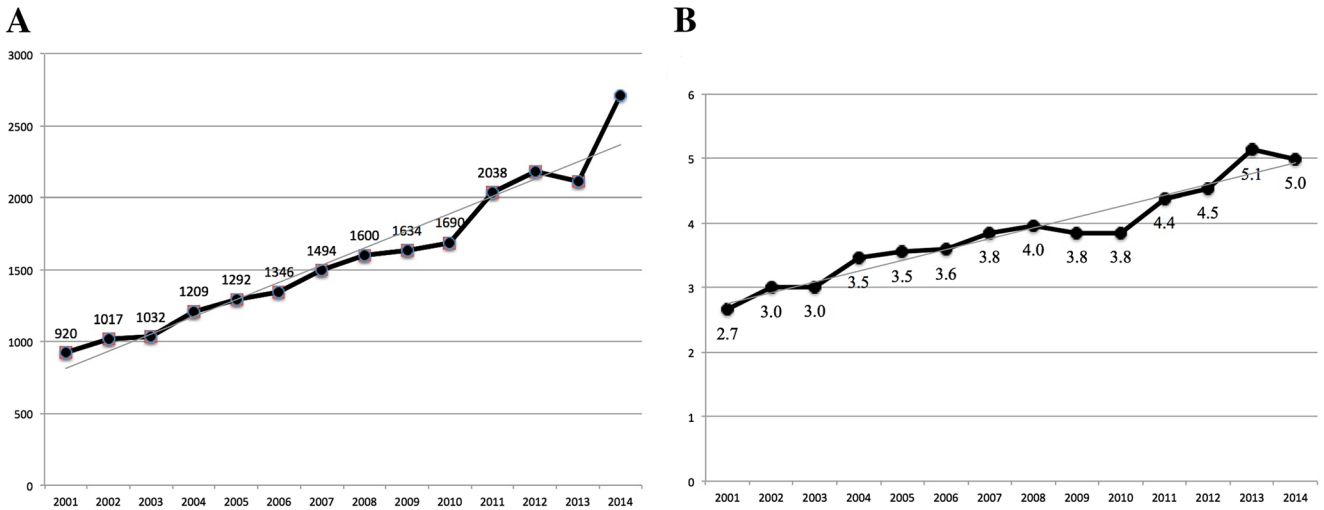

Fig. 1 Full articles in English published during 2013 and previous years were retrieved from PubMed using the search word 'autoimmunity'. The yearly trends in absolute numbers (**a**) and as ratio within publications retrieved using 'immunology' (**b**) are represented

some articles for further discussion. Among the numerous possibilities, this year, we evaluated new developments in specific clinical settings, i.e., autoimmune and chronic inflammatory diseases, along with common mechanisms which are gathering significant scientific support and point to a therapeutic use. We are well-aware that this choice implies that data on rare and orphan conditions are overlooked [2], as in the case of Behcet disease [3–8], relapsing polychondritis [9, 10], vasculitidies [11–16], myasthenia gravis [17–20], primary immunodeficiencies [21, 22], and others [3, 23–35]. Furthermore, we chose not to address the intriguing field of autoimmunity and cancer which is 2014 has been the subject of numerous studies [36–40].

Systemic lupus erythematosus (SLE)

The literature on systemic lupus erythematosus (SLE) during 2014 covered numerous aspects of this complex disease which remain the paradigm for the overlap between internal medicine and rheumatology [41] with variable clinical manifestations [42, 43] and epidemiology which was analyzed in France [44], while clinical patterns may be variable across countries, as illustrated by data from an international European registry [45] and by data on the genetic susceptibility in the Chinese [46, 47] and other populations [48]. Despite recent progress with effective biologics and classical treatments [49], there is a significant unmet need for new therapeutic targets in SLE [50]. Importantly, reports illustrate that the major remaining outcome which most significantly affects survival of patients with SLE is the cardiovascular risk [51] while in a subgroup of patients the risk of specific cancers could be elevated [52]. In the case of thrombotic events, one should rule out the presence of anti-phospholipid syndrome [53] which, while straightforward in cases with typical serological profiles, may be challenging during the acute phases and warrant a specific treatment with recent encouraging data on the protective effects of aspirin [54]. In this group of patients, recent international meetings provided an update on the treatment guidelines [55–57] while more attention should be provided to the most severe forms such as pediatric [58] and neurological cases [59] as well as the classical obstetric manifestations [60]. Recent data also continue to support the direct pathogenetic role of anti-phospholipid antibodies [61], particularly those directed at beta-2 glycoprotein I [62] which may be targeted with elegant treatments [63]. Further, reports suggest new non-invasive tools such as fetal DNA to screen for potential complications [64], that different serum autoantibodies may be associated with the thrombotic risk [65, 66], while the syndrome could be mediated by T regulatory cells [67]. Remaining on clinical grounds, we welcome a comprehensive evaluation of the challenging differential diagnosis with drug-induced autoimmune manifestations [68], mixed connective tissue disease [69], or other conditions including infections and malignancies [70] and the viewpoints provided on the safety and effectiveness of vaccinations in patients with SLE [71]. Translational evidence in the broad field of SLE includes the identification of serum anti-ribosomal-P autoantibodies influencing the renal manifestations [72] similar to the classical anti-double stranded DNA autoantibodies for which a pathogenetic role is strongly supported [73], the role of B cell DNA methylation of specific genes [74] within the broad area of the epigenetics [75–77] and signaling [78] in SLE and the possible links with cytokine alterations [79, 80], possibly through genetic polymorphisms of the oncostatin M receptor (OSMR) activating JAK/STAT and MAPK pathways, and the central role of B cells in disease perpetuation [81]. Among new candidates for SLE initiation and modulation, we should

mention the hypotheses related to parasitic [82, 83] or other infections [84] while the study of microRNA and epigenetics [85–87], or IL17 contribution to disease pathogenesis [88–90], remains a hot topic in SLE. Of relevance to SLE, the study of Sjogren syndrome [91–93] provides important clinical observations related to common reproductive factors [94] and diagnostic imaging methods [95]. From an experimental standpoint, data in this related connective tissue disease support the role of autoreactive T cells [96, 97], double negative T cells [98], autoantigen expression in target tissues [99], Th17 cells [100], or candidate biomarkers of disease [101].

Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) continues to drive a significant amount of research from both basic and clinical groups, and the novel reevaluation of patient classification should be considered when comparing past and future results in patients arrayed according to different criteria [102] or the possible overlapping with other conditions with different clinical manifestations [103, 104] or age of onset [105, 106] with possible diagnostic challenges with seronegative arthritides [107–109]. We may also expect that laboratory data connection with the disease phenotype will continue to gain importance, as demonstrated for genetics [110] and serum autoantibodies against citrullinated peptides [111, 112]. Furthermore, we also read with great interest the newest literature on less common and potentially threatening manifestations such as the cervical vertebral involvement [113] and the cardiac arrhythmias linked to chronic inflammation [114]. Laboratory research pointed at specific features of RA with the identification of new IL17-dependent mechanisms of bone resorption [115], B cell activation profiles in the presence of B cell depleting treatments such as rituximab [116], unexpected links between innate immunity via toll like receptors [117] and synoviocytes [118], and the role of posttranslational modification in autoantigen establishment [119]. Possibly more than in any other rheumatic disease, our therapeutic armamentarium to treat RA has grown significantly over the past decade [120, 121] with numerous biologics now targeting pro-inflammatory molecules such as TNFalpha or IL6 [122], or cell costimulation which may result in a more prominent effect in early stages [123]. A better definition of the safety and efficacy profiles of these treatments is now established [124, 125], and data on biosimilars are awaited to define the clear positioning of these less expensive treatments in the therapeutic flowchart [126], and a fine immunological typing of patients to chose the best treatment remains the ultimate goal [127]. We should underline that methotrexate remains the backbone of any biologic treatment for RA with acceptable safety [128], and data on drug retention confirm the synergy between classical and biological treatments [129] with possible new mechanisms [130]. Finally, it is intriguing that less obvious factors involved in RA onset and perpetuation include obesity [131] and the socioeconomic status [132], although a direct cause-effect relationship is difficult to establish, and we may submit that new evidence in the next months will point to new cytokines [133–136] and chemokines [137] or new genetic functional testing [138, 139] for autoimmunity and RA.

Seronegative arthritides

Despite the jury being still out on the autoimmune features of seronegative spondyloarthropathies, we are convinced that the skin, articular, metabolic, and systemic manifestations of this condition represent a continuum [107, 108, 140] in which similarities with autoimmune diseases (especially rheumatoid arthritis) significantly outnumber differences, similar to inflammatory bowel disease [109, 141–147]. Indeed, the recent progress in the understanding of the pathogenesis of psoriatic disease represents a significant breakthrough which is rapidly opening new therapeutic avenues, as in the case of treatments targeting the IL12/IL23 axis [148], IL17 [149, 150], or other molecular mechanisms [151]. We are particularly intrigued by the recent statements from a joint multispecialist effort to target these conditions which, as in the case of skin or gut manifestations, represent the ideal arena for a multidisciplinary management [152].

Conclusions and hopes for the current year

During the year 2014, we were particularly intrigued by the new scenarios appearing in the field and by the capacity of researchers and physicians worldwide to provide comprehensive reviews and recommendations in the most popular areas of clinical and research activity. As mentioned, this was mirrored by a surprising increase in the number of published articles which may, however, not constitute the ideal marker for the activity and success in this research area. As we have done in the previous years, we herein attempted to provide a bird's eye view of arbitrarily selected articles that were published in 2014. Nonetheless, we feel that other overlooked reports from our literature search may prove key to future discoveries. Among these, new developments are expected to stem from the interaction between T regulatory cells and B cell anergy in lupus models [81], the role of IL4 in B cell maturation [153], the network connecting innate immunity with autoimmunity via TLRs [36, 117, 154–159], the growing role of the PTPN22 kinase [17, 138, 139, 160, 161], or the new data on T regulatory cells [162] or T cell receptors [163, 164]. While we cannot foresee the number of publications related to autoimmunity in 2015, it is to be expected that new data will be possibly more intriguing compared to 2014.

References

1. Selmi C (2014) Autoimmunity in 2013. Clin Rev Allergy Immunol 47:100–109
2. Dias C, Selmi C (2014) The challenge of treating orphan disease. Clin Rev Allergy Immunol 47:259–263
3. Caso F, Costa L, Rigante D et al (2014) Caveats and truths in genetic, clinical, autoimmune and autoinflammatory issues in Blau syndrome and early onset sarcoidosis. Autoimmun Rev 13: 1220–1229
4. Comarmond C, Wechsler B, Bodaghi B, Cacoub P, Saadoun D (2014) Biotherapies in Behcet's disease. Autoimmun Rev 13: 762–769
5. Ozyazgan Y, Ucar D, Hatemi G, Yazici Y (2014) Ocular involvement of Behcet's syndrome: a comprehensive review. Clin Rev Allergy Immunol. doi:10.1007/s12016-014-8425-z
6. Schwartzman S, Schwartzman M (2014) The use of biologic therapies in Uveitis. Clin Rev Allergy Immunol. doi:10.1007/s12016-014-8455-6
7. Selmi C (2014) Diagnosis and classification of autoimmune uveitis. Autoimmun Rev 13:591–594
8. Yazici H, Yazici Y (2014) Criteria for Behcet's disease with reflections on all disease criteria. J Autoimmun 48–49:104–107
9. Cantarini L, Vitale A, Brizi MG et al (2014) Diagnosis and classification of relapsing polychondritis. J Autoimmun 48–49:53–59
10. Arnaud L, Mathian A, Haroche J, Gorochov G, Amoura Z (2014) Pathogenesis of relapsing polychondritis: a 2013 update. Autoimmun Rev 13:90–95
11. Thai LH, Charles P, Resche-Rigon M, Desseaux K, Guillevin L (2014) Are anti-proteinase-3 ANCA a useful marker of granulomatosis with polyangiitis (Wegener's) relapses? Results of a retrospective study on 126 patients. Autoimmun Rev 13:313–318
12. Mouthon L, Dunogue B, Guillevin L (2014) Diagnosis and classification of eosinophilic granulomatosis with polyangiitis (formerly named Churg-Strauss syndrome). J Autoimmun 48–49:99–103
13. Monti G, Saccardo F, Castelnovo L et al (2014) Prevalence of mixed cryoglobulinaemia syndrome and circulating cryoglobulins in a population-based survey: the Origgio study. Autoimmun Rev 13:609–614
14. Chimenti MS, Ballanti E, Triggianese P, Perricone R (2014) Vasculitides and the complement system: a comprehensive review. Clin Rev Allergy Immunol. doi:10.1007/s12016-014-8453-8
15. Comarmond C, Cacoub P (2014) Granulomatosis with polyangiitis (Wegener): clinical aspects and treatment. Autoimmun Rev 13: 1121–1125
16. Hellmark T, Segelmark M (2014) Diagnosis and classification of Goodpasture's disease (anti-GBM). J Autoimmun 48–49:108–112
17. Avidan N, Le Panse R, Berrih-Aknin S, Miller A (2014) Genetic basis of myasthenia gravis—a comprehensive review. J Autoimmun 52:146–153
18. Berrih-Aknin S, Le Panse R (2014) Myasthenia gravis: a comprehensive review of immune dysregulation and etiological mechanisms. J Autoimmun 52:90–100
19. Berrih-Aknin S, Frenkian-Cuvelier M, Eymard B (2014) Diagnostic and clinical classification of autoimmune myasthenia gravis. J Autoimmun 48–49:143–148
20. Berrih-Aknin S (2014) Myasthenia Gravis: paradox versus paradigm in autoimmunity. J Autoimmun 52:1–28
21. Hernandez-Trujillo V (2014) New genetic discoveries and primary immune deficiencies. Clin Rev Allergy Immunol 46:145–153
22. Ballow M (2014) Historical perspectives in the diagnosis and treatment of primary immune deficiencies. Clin Rev Allergy Immunol 46:101–103
23. Cutolo M (2014) Autoimmune polyendocrine syndromes. Autoimmun Rev 13:85–89
24. Ben-Dov I, Segel MJ (2014) Autoimmune pulmonary alveolar proteinosis: clinical course and diagnostic criteria. Autoimmun Rev 13:513–517
25. Betterle C, Garelli S, Presotto F (2014) Diagnosis and classification of autoimmune parathyroid disease. Autoimmun Rev 13: 417–422
26. Bizzaro N, Antico A (2014) Diagnosis and classification of pernicious anemia. Autoimmun Rev 13:565–568
27. Bowlus CL, Gershwin ME (2014) The diagnosis of primary biliary cirrhosis. Autoimmun Rev 13:441–444
28. Braithwaite T, Holder GE, Lee RW, Plant GT, Tufail A (2014) Diagnostic features of the autoimmune retinopathies. Autoimmun Rev 13:534–538
29. Brandao Neto RA, de Carvalho JF (2014) Diagnosis and classification of Addison's disease (autoimmune adrenalitis). Autoimmun Rev 13:408–411
30. Burke RJ, Chang C (2014) Diagnostic criteria of acute rheumatic fever. Autoimmun Rev 13:503–507
31. Chang HH, Chiang BL (2014) The diagnosis and classification of autoimmune coagulopathy: an updated review. Autoimmun Rev 13:587–590
32. Greco A, De Virgilio A, Gallo A et al (2014) Susac's syndrome—pathogenesis, clinical variants and treatment approaches. Autoimmun Rev 13:814–821
33. Zhao H, Zhang Y, Xiao G, Wu N, Xu J, Fang Z (2014) Interleukin-18 gene promoter—607 A/C polymorphism and the risk of immune thrombocytopenia. Autoimmunity 47:478–481
34. Goebel A (2014) Immune activation and autoimmunity in chronic pain conditions and response to immunoglobulin G. Clin Exp Immunol 178(Suppl 1):39–41
35. Jarius S, Wildemann B, Paul F (2014) Neuromyelitis optica: clinical features, immunopathogenesis and treatment. Clin Exp Immunol 176:149–164
36. Cohen IR (2014) Activation of benign autoimmunity as both tumor and autoimmune disease immunotherapy: a comprehensive review. J Autoimmun 54:112–117
37. Saito Y, Saito H, Liang G, Friedman JM (2014) Epigenetic alterations and microRNA misexpression in cancer and autoimmune diseases: a critical review. Clin Rev Allergy Immunol 47:128–135
38. Colaci M, Giuggioli D, Vacchi C et al (2014) Breast cancer in systemic sclerosis: results of a cross-linkage of an Italian Rheumatologic Center and a population-based Cancer Registry and review of the literature. Autoimmun Rev 13:132–137
39. Bernal-Bello D, Garcia de Tena J, Simeon-Aznar C, Fonollosa-Pla V (2014) Systemic sclerosis, breast cancer and calcium channel blockers: a new player on the scene? Autoimmun Rev 13:880–881
40. Klarquist J, Hennies CM, Lehn MA, Reboulet RA, Feau S, Janssen EM (2014) STING-mediated DNA sensing promotes antitumor and autoimmune responses to dying cells. J Immunol 193: 6124–6134
41. Selmi C (2014) Hot topics in autoimmune diseases: perspectives from the 2013 Asian Congress of Autoimmunity. Autoimmun Rev 13:781–787
42. Kuhn A, Landmann A (2014) The classification and diagnosis of cutaneous lupus erythematosus. J Autoimmun 48–49:14–19
43. Yu C, Gershwin ME, Chang C (2014) Diagnostic criteria for systemic lupus erythematosus: a critical review. J Autoimmun 48–49: 10–13
44. Arnaud L, Fagot JP, Mathian A, Paita M, Fagot-Campagna A, Amoura Z (2014) Prevalence and incidence of systemic lupus erythematosus in France: a 2010 nation-wide population-based study. Autoimmun Rev 13:1082–1089
45. Cervera R, Doria A, Amoura Z et al (2014) Patterns of systemic lupus erythematosus expression in Europe. Autoimmun Rev 13: 621–629

46. Cheng FJ, Zhou XJ, Zhao YF, Zhao MH, Zhang H (2014) Chemokine receptor 5 (CCR5) delta 32 polymorphism in lupus nephritis: a large case–control study and meta-analysis. Autoimmunity 47:383–388
47. Ni J, Zhang M, Zhu Y et al (2014) Association study of interleukin-19 rs2243188 polymorphism with systemic lupus erythematosus in a Chinese population. Autoimmunity 47:378–382
48. Vigato-Ferreira IC, Toller-Kawahisa JE, Pancoto JA et al (2014) FcgammaRIIa and FcgammaRIIIb polymorphisms and associations with clinical manifestations in systemic lupus erythematosus patients. Autoimmunity 47:451–458
49. Ruiz-Irastorza G, Danza A, Perales I et al (2014) Prednisone in lupus nephritis: how much is enough? Autoimmun Rev 13: 206–214
50. Sthoeger Z, Sharabi A, Mozes E (2014) Novel approaches to the development of targeted therapeutic agents for systemic lupus erythematosus. J Autoimmun 54:60–71
51. Gustafsson JT, Svenungsson E (2014) Definitions of and contributions to cardiovascular disease in systemic lupus erythematosus. Autoimmunity 47:67–76
52. Zard E, Arnaud L, Mathian A et al (2014) Increased risk of high grade cervical squamous intraepithelial lesions in systemic lupus erythematosus: A meta-analysis of the literature. Autoimmun Rev 13:730–735
53. Gomez-Puerta JA, Cervera R (2014) Diagnosis and classification of the antiphospholipid syndrome. J Autoimmun 48–49:20–25
54. Arnaud L, Mathian A, Ruffatti A et al (2014) Efficacy of aspirin for the primary prevention of thrombosis in patients with antiphospholipid antibodies: an international and collaborative meta-analysis. Autoimmun Rev 13:281–291
55. Cervera R, Rodriguez-Pinto I, Colafrancesco S et al (2014) 14th International Congress on Antiphospholipid Antibodies Task Force Report on Catastrophic Antiphospholipid Syndrome. Autoimmun Rev 13:699–707
56. de Jesus GR, Agmon-Levin N, Andrade CA et al (2014) 14th International Congress on Antiphospholipid Antibodies Task Force report on obstetric antiphospholipid syndrome. Autoimmun Rev 13:795–813
57. Erkan D, Aguiar CL, Andrade D et al (2014) 14th International Congress on Antiphospholipid Antibodies: task force report on antiphospholipid syndrome treatment trends. Autoimmun Rev 13:685–696
58. Berman H, Rodriguez-Pinto I, Cervera R et al (2014) Pediatric catastrophic antiphospholipid syndrome: descriptive analysis of 45 patients from the "CAPS Registry". Autoimmun Rev 13:157–162
59. Jeltsch-David H, Muller S (2014) Neuropsychiatric systemic lupus erythematosus and cognitive dysfunction: the MRL-lpr mouse strain as a model. Autoimmun Rev 13:963–973
60. D'Ippolito S, Meroni PL, Koike T, Veglia M, Scambia G, Di Simone N (2014) Obstetric antiphospholipid syndrome: a recent classification for an old defined disorder. Autoimmun Rev 13: 901–908
61. Katzav A, Menachem A, Maggio N, Pollak L, Pick CG, Chapman J (2014) IgG accumulates in inhibitory hippocampal neurons of experimental antiphospholipid syndrome. J Autoimmun 55:86–93
62. Raschi E, Chighizola CB, Grossi C et al (2014) beta2-glycoprotein I, lipopolysaccharide and endothelial TLR4: three players in the two hit theory for anti-phospholipid-mediated thrombosis. J Autoimmun 55:42–50
63. Zandman-Goddard G, Pierangeli SS, Gertel S, Blank M (2014) Tolerogenic dendritic cells specific for beta2-glycoprotein-I Domain-I, attenuate experimental antiphospholipid syndrome. J Autoimmun 54:72–80
64. Korabecna M, Ulcova-Gallova Z, Horinek A, Pazourkova E, Calda P (2014) Quantification of circulating fetal DNA as a tool for potential monitoring of pregnant patients with antiphospholipid antibodies. Autoimmunity 47:473–477
65. Reynaud Q, Lega JC, Mismetti P et al (2014) Risk of venous and arterial thrombosis according to type of antiphospholipid antibodies in adults without systemic lupus erythematosus: a systematic review and meta-analysis. Autoimmun Rev 13:595–608
66. Tozzoli R, Villalta D (2014) Autoantibody profiling of patients with antiphospholipid syndrome using an automated multiplexed immunoassay system. Autoimmun Rev 13:59–63
67. Staub HL, Dal Ben ER, Bauer ME (2014) The antiphospholipid syndrome and Tregs. Autoimmun Rev 13:697–698
68. Xiao X, Chang C (2014) Diagnosis and classification of drug-induced autoimmunity (DIA). J Autoimmun 48–49:66–72
69. Tani C, Carli L, Vagnani S et al (2014) The diagnosis and classification of mixed connective tissue disease. J Autoimmun 48–49: 46–49
70. Calixto OJ, Franco JS, Anaya JM (2014) Lupus mimickers. Autoimmun Rev 13:865–872
71. Murdaca G, Orsi A, Spano F et al (2014) Influenza and pneumococcal vaccinations of patients with systemic lupus erythematosus: current views upon safety and immunogenicity. Autoimmun Rev 13:75–84
72. Ben-Ami Shor D, Blank M, Reuter S et al (2014) Anti-ribosomal-P antibodies accelerate lupus glomerulonephritis and induce lupus nephritis in naive mice. J Autoimmun 54:118–126
73. Gesheva V, Kerekov N, Nikolova K et al (2014) Suppression of dsDNA-specific B lymphocytes reduces disease symptoms in SCID model of mouse lupus. Autoimmunity 47:162–172
74. Fali T, Le Dantec C, Thabet Y et al (2014) DNA methylation modulates HRES1/p28 expression in B cells from patients with Lupus. Autoimmunity 47:265–271
75. Hedrich CM, Crispin JC, Tsokos GC (2014) Epigenetic regulation of cytokine expression in systemic lupus erythematosus with special focus on T cells. Autoimmunity 47:234–241
76. Liu A, La Cava A (2014) Epigenetic dysregulation in systemic lupus erythematosus. Autoimmunity 47:215–219
77. Oaks Z, Perl A (2014) Metabolic control of the epigenome in systemic Lupus erythematosus. Autoimmunity 47:256–264
78. Liang Y, Xu WD, Yang XK et al (2014) Association of signaling transducers and activators of transcription 1 and systemic lupus erythematosus. Autoimmunity 47:141–145
79. Kuhn A, Wenzel J, Weyd H (2014) Photosensitivity, apoptosis, and cytokines in the pathogenesis of lupus erythematosus: a critical review. Clin Rev Allergy Immunol 47:148–162
80. Tang X, Zhang B, Jarrell JA et al (2014) Ly108 expression distinguishes subsets of invariant NKT cells that help autoantibody production and secrete IL-21 from those that secrete IL-17 in lupus prone NZB/W mice. J Autoimmun 50:87–98
81. Liu Y, Liu A, Iikuni N, Xu H, Shi FD, La Cava A (2014) Regulatory CD4+ T cells promote B cell anergy in murine lupus. J Immunol 192:4069–4073
82. Miyake K, Adachi K, Watanabe M et al (2014) Parasites alter the pathological phenotype of lupus nephritis. Autoimmunity 47:538–547
83. Maizels RM, McSorley HJ, Smyth DJ (2014) Helminths in the hygiene hypothesis: sooner or later? Clin Exp Immunol 177:38–46
84. Rigante D, Mazzoni MB, Esposito S (2014) The cryptic interplay between systemic lupus erythematosus and infections. Autoimmun Rev 13:96–102
85. Zan H (2014) Epigenetics in lupus. Autoimmunity 47:213–214
86. Zan H, Tat C, Casali P (2014) MicroRNAs in lupus. Autoimmunity 47:272–285
87. Rogatsky I, Chandrasekaran U, Manni M, Yi W, Pernis AB (2014) Epigenetics and the IRFs: a complex interplay in the control of immunity and autoimmunity. Autoimmunity 47:242–255

88. Summers SA, Odobasic D, Khouri MB et al (2014) Endogenous interleukin (IL)-17A promotes pristane-induced systemic autoimmunity and lupus nephritis induced by pristane. Clin Exp Immunol 176:341–350
89. Wei R, Dong L, Xiao Q, Sun D, Li X, Nian H (2014) Engagement of Toll-like receptor 2 enhances interleukin (IL)-17(+) autoreactive T cell responses via p38 mitogen-activated protein kinase signalling in dendritic cells. Clin Exp Immunol 178: 353–363
90. Zhong J, Yu Q, Yang P et al (2014) MBD2 regulates TH17 differentiation and experimental autoimmune encephalomyelitis by controlling the homeostasis of T-bet/Hlx axis. J Autoimmun 53: 95–104
91. Seror R, Theander E, Bootsma H et al (2014) Outcome measures for primary Sjogren's syndrome: a comprehensive review. J Autoimmun 51:51–56
92. Moutsopoulos HM (2014) Sjogren's syndrome: a forty-year scientific journey. J Autoimmun 51:1–9
93. Goules AV, Tzioufas AG, Moutsopoulos HM (2014) Classification criteria of Sjogren's syndrome. J Autoimmun 48–49:42–45
94. De Carolis S, Salvi S, Botta A et al (2014) The impact of primary Sjogren's syndrome on pregnancy outcome: our series and review of the literature. Autoimmun Rev 13:103–107
95. Ziakas PD, Poulou LS, Thanos L (2014) Towards integrating positron emission tomography for work-up of patients with Sjogren's syndrome and associated lymphomas. Autoimmun Rev 13:327–329
96. Sumida T, Tsuboi H, Iizuka M, Hirota T, Asashima H, Matsumoto I (2014) The role of M3 muscarinic acetylcholine receptor reactive T cells in Sjogren's syndrome: a critical review. J Autoimmun 51: 44–50
97. Moriyama M, Tanaka A, Maehara T, Furukawa S, Nakashima H, Nakamura S (2014) T helper subsets in Sjogren's syndrome and IgG4-related dacryoadenitis and sialoadenitis: a critical review. J Autoimmun 51:81–88
98. Alunno A, Carubbi F, Bistoni O et al (2014) CD4(−)CD8(−) T-cells in primary Sjogren's syndrome: association with the extent of glandular involvement. J Autoimmun 51:38–43
99. Aqrawi LA, Kvarnstrom M, Brokstad KA, Jonsson R, Skarstein K, Wahren-Herlenius M (2014) Ductal epithelial expression of Ro52 correlates with inflammation in salivary glands of patients with primary Sjogren's syndrome. Clin Exp Immunol 177: 244–252
100. Alunno A, Carubbi F, Bartoloni E et al (2014) Unmasking the pathogenic role of IL-17 axis in primary Sjogren's syndrome: a new era for therapeutic targeting? Autoimmun Rev 13:1167–1173
101. Quartuccio L, Isola M, Baldini C et al (2014) Biomarkers of lymphoma in Sjogren's syndrome and evaluation of the lymphoma risk in prelymphomatous conditions: results of a multicenter study. J Autoimmun 51:75–80
102. Kourilovitch M, Galarza-Maldonado C, Ortiz-Prado E (2014) Diagnosis and classification of rheumatoid arthritis. J Autoimmun 48–49:26–30
103. Mahroum N, Mahagna H, Amital H (2014) Diagnosis and classification of adult Still's disease. J Autoimmun 48–49:34–37
104. Maria AT, Le Quellec A, Jorgensen C, Touitou I, Riviere S, Guilpain P (2014) Adult onset Still's disease (AOSD) in the era of biologic therapies: dichotomous view for cytokine and clinical expressions. Autoimmun Rev 13:1149–1159
105. Nesher G (2014) Polymyalgia rheumatica—diagnosis and classification. J Autoimmun 48–49:76–78
106. Rigante D, Bosco A, Esposito S (2014) The etiology of juvenile idiopathic arthritis. Clin Rev Allergy Immunol. doi:10.1007/s12016-014-8460-9
107. Selmi C, Gershwin ME (2014) Diagnosis and classification of reactive arthritis. Autoimmun Rev 13:546–549
108. Raychaudhuri SP, Deodhar A (2014) The classification and diagnostic criteria of ankylosing spondylitis. J Autoimmun 48–49: 128–133
109. Atzeni F, Defendenti C, Ditto MC et al (2014) Rheumatic manifestations in inflammatory bowel disease. Autoimmun Rev 13:20–23
110. Lin YZ, Li RN, Lin CH et al (2014) Association of OSMR gene polymorphisms with rheumatoid arthritis and systemic lupus erythematosus patients. Autoimmunity 47:23–26
111. Sakkas LI, Bogdanos DP, Katsiari C, Platsoucas CD (2014) Anti-citrullinated peptides as autoantigens in rheumatoid arthritis-relevance to treatment. Autoimmun Rev 13:1114–1120
112. Muller S, Radic M (2014) Citrullinated autoantigens: from diagnostic markers to pathogenetic mechanisms. Clin Rev Allergy Immunol. doi:10.1007/s12016-014-8459-2
113. Joaquim AF, Appenzeller S (2014) Cervical spine involvement in rheumatoid arthritis—a systematic review. Autoimmun Rev 13: 1195–1202
114. Lazzerini PE, Capecchi PL, Acampa M, Galeazzi M, Laghi-Pasini F (2014) Arrhythmic risk in rheumatoid arthritis: the driving role of systemic inflammation. Autoimmun Rev 13:936–944
115. Caetano-Lopes J, Rodrigues A, Lopes A et al (2014) Rheumatoid arthritis bone fragility is associated with upregulation of IL17 and DKK1 gene expression. Clin Rev Allergy Immunol 47:38–45
116. Cambridge G, Perry HC, Nogueira L et al (2014) The effect of B-cell depletion therapy on serological evidence of B-cell and plasmablast activation in patients with rheumatoid arthritis over multiple cycles of rituximab treatment. J Autoimmun 50:67–76
117. Liu Y, Yin H, Zhao M, Lu Q (2014) TLR2 and TLR4 in autoimmune diseases: a comprehensive review. Clin Rev Allergy Immunol 47:136–147
118. Savic S, Ouboussad L, Dickie LJ et al (2014) TLR dependent XBP-1 activation induces an autocrine loop in rheumatoid arthritis synoviocytes. J Autoimmun 50:59–66
119. Zavala-Cerna MG, Martinez-Garcia EA, Torres-Bugarin O, Rubio-Jurado B, Riebeling C, Nava A (2014) The clinical significance of posttranslational modification of autoantigens. Clin Rev Allergy Immunol 47:73–90
120. Chang C (2014) Unmet needs in the treatment of autoimmunity: from aspirin to stem cells. Autoimmun Rev 13:331–346
121. Chighizola CB, Favalli EG, Meroni PL (2014) Novel mechanisms of action of the biologicals in rheumatic diseases. Clin Rev Allergy Immunol 47:6–16
122. Alghasham A, Rasheed Z (2014) Therapeutic targets for rheumatoid arthritis: Progress and promises. Autoimmunity 47:77–94
123. Caporali R, Bugatti S, Cavagna L, Antivalle M, Sarzi-Puttini P (2014) Modulating the co-stimulatory signal for T cell activation in rheumatoid arthritis: could it be the first step of the treatment? Autoimmun Rev 13:49–53
124. Kaltsonoudis E, Voulgari PV, Konitsiotis S, Drosos AA (2014) Demyelination and other neurological adverse events after anti-TNF therapy. Autoimmun Rev 13:54–58
125. Piga M, Chessa E, Ibba V et al (2014) Biologics-induced autoimmune renal disorders in chronic inflammatory rheumatic diseases: systematic literature review and analysis of a monocentric cohort. Autoimmun Rev 13:873–879
126. Fiorino G, Girolomoni G, Lapadula G et al (2014) The use of biosimilars in immune-mediated disease: A joint Italian Society of Rheumatology (SIR), Italian Society of Dermatology (SIDeMaST), and Italian Group of Inflammatory Bowel Disease (IG-IBD) position paper. Autoimmun Rev 13:751–755
127. Sozzani S, Abbracchio MP, Annese V et al (2014) Chronic inflammatory diseases: do immunological patterns drive the choice of biotechnology drugs? A critical review. Autoimmunity 47:287–306

128. Kivity S, Zafrir Y, Loebstein R, Pauzner R, Mouallem M, Mayan H (2014) Clinical characteristics and risk factors for low dose methotrexate toxicity: a cohort of 28 patients. Autoimmun Rev 13:1109–1113
129. Favalli EG, Biggioggero M, Meroni PL (2014) Methotrexate for the treatment of rheumatoid arthritis in the biologic era: still an "anchor" drug? Autoimmun Rev 13:1102–1108
130. Pigott E, DuHadaway JB, Muller AJ, Gilmour S, Prendergast GC, Mandik-Nayak L (2014) 1-Methyl-tryptophan synergizes with methotrexate to alleviate arthritis in a mouse model of arthritis. Autoimmunity 47:409–418
131. Versini M, Jeandel PY, Rosenthal E, Shoenfeld Y (2014) Obesity in autoimmune diseases: not a passive bystander. Autoimmun Rev 13:981–1000
132. Calixto OJ, Anaya JM (2014) Socioeconomic status. The relationship with health and autoimmune diseases. Autoimmun Rev 13: 641–654
133. Sattler S, Ling GS, Xu D et al (2014) IL-10-producing regulatory B cells induced by IL-33 (Breg(IL-33)) effectively attenuate mucosal inflammatory responses in the gut. J Autoimmun 50:107–122
134. Yang X, Zheng SG (2014) Interleukin-22: a likely target for treatment of autoimmune diseases. Autoimmun Rev 13:615–620
135. Chevalier N, Thorburn AN, Macia L et al (2014) Inflammation and lymphopenia trigger autoimmunity by suppression of IL-2-controlled regulatory T cell and increase of IL-21-mediated effector T cell expansion. J Immunol 193:4845–4858
136. Bessa J, Meyer CA, de Vera Mudry MC et al (2014) Altered subcellular localization of IL-33 leads to non-resolving lethal inflammation. J Autoimmun 55:33–41
137. Antonelli A, Ferrari SM, Giuggioli D, Ferrannini E, Ferri C, Fallahi P (2014) Chemokine (C-X-C motif) ligand (CXCL)10 in autoimmune diseases. Autoimmun Rev 13:272–280
138. Maine CJ, Marquardt K, Cheung J, Sherman LA (2014) PTPN22 controls the germinal center by influencing the numbers and activity of T follicular helper cells. J Immunol 192:1415–1424
139. Zheng J, Petersen F, Yu X (2014) The role of PTPN22 in autoimmunity: learning from mice. Autoimmun Rev 13:266–271
140. Raychaudhuri SK, Maverakis E, Raychaudhuri SP (2014) Diagnosis and classification of psoriasis. Autoimmun Rev 13:490–495
141. Ben-Horin S, Kopylov U, Chowers Y (2014) Optimizing anti-TNF treatments in inflammatory bowel disease. Autoimmun Rev 13:24–30
142. Cassinotti A, Sarzi-Puttini P, Fichera M, Shoenfeld Y, de Franchis R, Ardizzone S (2014) Immunity, autoimmunity and inflammatory bowel disease. Autoimmun Rev 13:1–2
143. Conrad K, Roggenbuck D, Laass MW (2014) Diagnosis and classification of ulcerative colitis. Autoimmun Rev 13:463–466
144. Fiorino G, Danese S, Pariente B, Allez M (2014) Paradoxical immune-mediated inflammation in inflammatory bowel disease patients receiving anti-TNF-alpha agents. Autoimmun Rev 13: 15–19
145. Geremia A, Biancheri P, Allan P, Corazza GR, Di Sabatino A (2014) Innate and adaptive immunity in inflammatory bowel disease. Autoimmun Rev 13:3–10
146. Monteleone G, Caruso R, Pallone F (2014) Targets for new immunomodulation strategies in inflammatory bowel disease. Autoimmun Rev 13:11–14
147. Laass MW, Roggenbuck D, Conrad K (2014) Diagnosis and classification of Crohn's disease. Autoimmun Rev 13:467–471
148. Suzuki E, Mellins ED, Gershwin ME, Nestle FO, Adamopoulos IE (2014) The IL-23/IL-17 axis in psoriatic arthritis. Autoimmun Rev 13:496–502
149. Novelli L, Chimenti MS, Chiricozzi A, Perricone R (2014) The new era for the treatment of psoriasis and psoriatic arthritis: perspectives and validated strategies. Autoimmun Rev 13:64–69
150. Singh RP, Hasan S, Sharma S et al (2014) Th17 cells in inflammation and autoimmunity. Autoimmun Rev 13:1174–1181
151. Kundu-Raychaudhuri S, Chen YJ, Wulff H, Raychaudhuri SP (2014) Kv1.3 in psoriatic disease: PAP-1, a small molecule inhibitor of Kv1.3 is effective in the SCID mouse psoriasis—xenograft model. J Autoimmun 55:63–72
152. Olivieri I, Cantini F, Castiglione F et al (2014) Italian Expert Panel on the management of patients with coexisting spondyloarthritis and inflammatory bowel disease. Autoimmun Rev 13:822–830
153. Granato A, Hayashi EA, Baptista BJ, Bellio M, Nobrega A (2014) IL-4 regulates Bim expression and promotes B cell maturation in synergy with BAFF conferring resistance to cell death at negative selection checkpoints. J Immunol 192:5761–5775
154. Seok H, Suh DW, Jo B et al (2014) Association between TLR1 polymorphisms and alopecia areata. Autoimmunity 47:372–377
155. Cordiglieri C, Marolda R, Franzi S et al (2014) Innate immunity in myasthenia gravis thymus: pathogenic effects of Toll-like receptor 4 signaling on autoimmunity. J Autoimmun 52:74–89
156. Cufi P, Soussan P, Truffault F et al (2014) Thymoma-associated myasthenia gravis: On the search for a pathogen signature. J Autoimmun 52:29–35
157. Guerrier T, Pochard P, Lahiri A, Youinou P, Pers JO, Jamin C (2014) TLR9 expressed on plasma membrane acts as a negative regulator of human B cell response. J Autoimmun 51:23–29
158. Manoharan I, Hong Y, Suryawanshi A et al (2014) TLR2-dependent activation of beta-catenin pathway in dendritic cells induces regulatory responses and attenuates autoimmune inflammation. J Immunol 193:4203–4213
159. Soni C, Wong EB, Domeier PP et al (2014) B cell-intrinsic TLR7 signaling is essential for the development of spontaneous germinal centers. J Immunol 193:4400–4414
160. Wiede F, Ziegler A, Zehn D, Tiganis T (2014) PTPN2 restrains CD8(+) T cell responses after antigen cross-presentation for the maintenance of peripheral tolerance in mice. J Autoimmun 53: 105–114
161. Salmond RJ, Brownlie RJ, Morrison VL, Zamoyska R (2014) The tyrosine phosphatase PTPN22 discriminates weak self peptides from strong agonist TCR signals. Nat Immunol 15:875–883
162. Levine AG, Arvey A, Jin W, Rudensky AY (2014) Continuous requirement for the TCR in regulatory T cell function. Nat Immunol 15:1070–1078
163. Zang Y, Martinez L, Fernandez I, Pignac-Kobinger J, Greidinger EL (2014) Conservation of pathogenic TCR homology across class II restrictions in anti-ribonucleoprotein autoimmunity: extended efficacy of T cell vaccine therapy. J Immunol 192: 4093–4102
164. Hogquist KA, Jameson SC (2014) The self-obsession of T cells: how TCR signaling thresholds affect fate 'decisions' and effector function. Nat Immunol 15:815–823