Clinic Rev Allerg Immunol (2016) 51:110–119
DOI 10.1007/s12016-016-8576-1

Autoimmunity in 2015

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Published online: 15 July 2016

Abstract Compared to the clear trend observed in previous years, the number of peer-reviewed articles published during 2015 and retrieved using the "autoimmunity" key word declined by 4 %, while remaining 5 % of immunology articles. On the other hand, a more detailed analysis of the published articles in leading immunology and autoimmunity journals revealed exciting scenarios, with fascinating lines of evidence being supported by convincing data and likely followed by rapid translational or clinical developments. As examples, the study of the microbiome, the development of new serum or other tissue biomarkers, and a more solid understanding of disease pathogenesis and tolerance breakdown mechanisms have been central issues in the past year. Furthermore and similar to the oncology field, progress in the understanding of single autoimmune condition is becoming most specific with psoriatic and rheumatoid arthritis being ideal paradigms with treatment options diverging after decades of common therapies, as illustrated by IL17-targeting approaches. The ultimate result of these advances is towards personalized medicine with an ideal approach being tailored on a single patient, based on a finely tuned definition of the immunogenetics, epigenetics, microbiome, and biomarkers. Finally, experimental reports suggest that cancer-associated immune mechanisms or the role of T and B cell subpopulations should be better understood in autoimmune diseases. While we hailed the 2014 literature in the autoimmunity world as part of an *annus mirabilis*, we should not be mistaken in the strong stimulus of research in autoimmunity represented by the 2015 articles that will be summarized in this article.

Keywords Tolerance breakdown · Genetics · Immunogenetics · Epigenetics · Microbiome · Th17 · Rheumatoid arthritis · Psoriasis · Psoriatic arthritis · Systemic lupus erythematosus · Multiple sclerosis

Was 2015 a Regular Year in Autoimmunity?

One year ago [1] and in previous years, we provided an overview of the publications dedicated to autoimmunity over 12 months and in 2015 confirmed a steady growth in the absolute number of papers on PubMed. The 2014 scenario was most surprising with the highest increase in the absolute number of publications (+28 %) compared to 2013 with a stable ratio with the immunology publications around 5 %. This year, a PubMed search was performed in May 2016 and retrieved 2595 articles published in English between January 1st and December 31st 2015 using "autoimmunity" as search word, and results are illustrated in Fig. 1. Among publications from 2015, we perused the major journals in the areas of immunology (*Nature Immunology*, *Nature Medicine*, *Clinical and Experimental Immunology*, *Clinical Reviews in Allergy and Immunology*) and autoimmunity (*Autoimmunity*, *Autoimmunity Reviews*, *Journal of Autoimmunity*) and arbitrarily selected those belonging to major clinical topics for further discussion. Quite obviously, this approach

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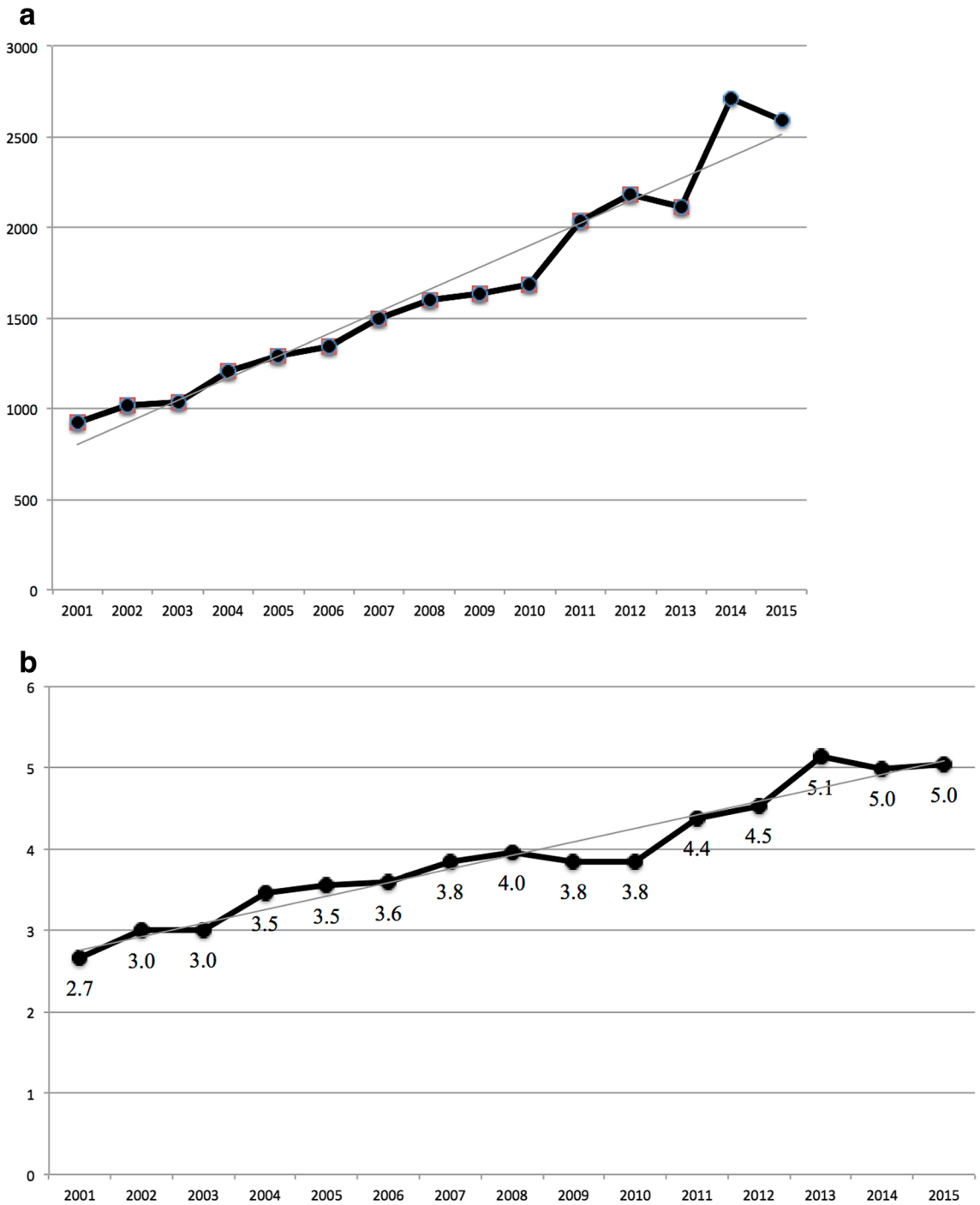

Fig. 1 Full articles (absolute number (**a**) and ratio with publications in "immunology" (**b**)) published during 2015 and previous years were retrieved from PubMed using the search word "autoimmunity" and the limit of English language

leads to an underrepresentation of rare disease [2–6], particularly vasculitidies [7–13] and sarcoidosis [14–22], or other fascinating issues such as the relationship with cancer both in terms of common mechanisms [23–26] or paraneoplastic autoimmunity [27–29]. Similarly, major cross-sectional issues are necessarily overlooked by the chosen approach, as well represented by T regulatory cells in the maintainance of peripheral tolerance [30–55] or new mechanisms of central tolerance, traditionally the subject of limited studies in human autoimmunity [55–66]. Quite interestingly, when we charted the number of 2015 publications including MeSH terms of major autoimmune diseases versus the reported highest prevalence rates [67], we observed a significant discrepancy with most frequent conditions being the subject of very few studies and vice versa (Fig. 2).

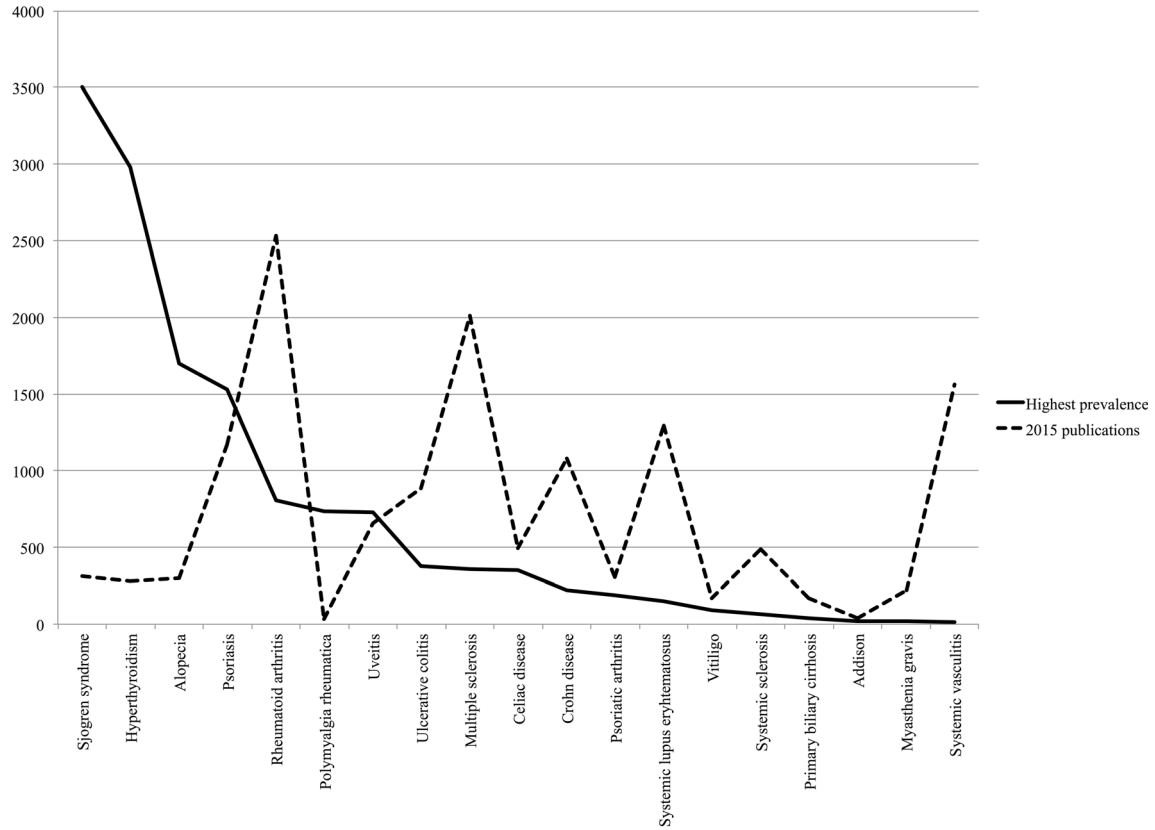

Fig. 2 The chart illustrates the number of 2015 publications including MeSH terms of major autoimmune diseases versus the reported highest prevalence rates (per 100.000). The figure is intended to be indicative of the lack of association between these two figures and necessarily includes epidemiological studies based on different case finding methods

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) remained a hot topic for research in 2015 with a vast number of experimental articles and reviews being devoted to the mechanisms and the clinical features of the disease. There is now agreement that SLE onset requires a genetic [68, 69] or immunogenetic [70, 71] susceptibility on which environmental factors, as in the case of the microbiota [72, 73], oxidative stress [74], and infectious agents [75], but apparently not adjuvants [76], may act and induce immunosenescence [77] and favor tolerance breakdown via other mechanisms [78–80], similar to what was observed in other connective tissue diseases [81]. From a clinical standpoint, there is a lively discussion on SLE clinimetrics or natural history [82–86] and data were presented on glucocorticoid receptors influence on SLE therapy outcomes, and the therapeutic use of regulatory T cells, mesenchymal stem cells, B-cells or natural killer cells [87], targeting FcalphaRI [88], inhibiting calcium/calmodulin-dependent protein kinase IV specific for CD4(+) T cells via a nanolipogel system [89], B cell depletion via rituximab [90] or epratuzumab [91], and high- or low-dose steroids [92]. Finally, promising data were presented with the use of helminth-derived tuftsin-phosphorylcholine which may modulate the immune response and prove beneficial in SLE [93] as in other autoimmune diseases [94]. On the other hand, there were major contributions on crucial issues such as reproductive health in women with SLE [95, 96] or the manifestations and treatment of antiphospholipid syndrome [97–101].

Among experimental articles, reports were of particular importance in dissecting the link between chronic inflammation and atherosclerosis in SLE. Black and Colleagues suggested that cholesterol may not be the only factor modulating inflammation and atherosclerosis in a normocholesterolemic lupus-prone mouse model [102], while others reported the increased recruitment of pro-inflammatory CD4+ CXCR3+ T cells into the arterial wall following IFN-alpha production by TLR 9-stimulated plasmacytoid dendritic cells [103], possibly via epigenetic mechanisms [104, 105] controlling type I INF [105] and other genes [74, 106], while IFN-gamma may also impact disease progression [107]. B cells and autoantibodies remain central to SLE pathogenesis and several experimental articles addressed this issue by investigating how pro-inflammatory factors, especially type I IFNalpha, are important in the B cell hyper-responsiveness to BCR crosslinking in SLE [108], the high number of B1 cells mediated by BLK expression [109], how, among numerous clinically relevant biomarkers [110–113], pentraxin 3 (PTX3)

[114] is expressed in lupus nephritis, primarily if anti-PTX3 antibodies are absent and correlates with fibrosis [115], how the BAFF receptor TACI may act as a promising therapeutic target [116].

Rheumatoid Arthritis and Spondyloarthritis

The field of chronic arthritis includes two major players in rheumatoid arthritis (RA) and spondyloarthritis (SpA) which recognize different pathogenesis and clinical features with less typical manifestations [117] or comorbidities [118, 119] in these systemic conditions. In the case of RA, major hints to etiology are derived from the high specificity of serum antibodies directed at citrullinated peptides since the earliest reports [117, 120, 121], with the subsequent migration of inflammatory cells, including osteoclasts [122], causing synovitis and erosions [123]. From a genetic standpoint, RA-associated polymorphisms are linked to functionally relevant phenotypes [124] and may help, along with different biomarkers such as microRNA [125] or long non-coding RNA [126], to array patients according to the disease manifestations, as in the case of bone erosions [127]. Ultimately, this personalization becomes of great importance in selecting the ideal therapeutic approach, considering the growing number of options [128], now including intravenous immunoglobulins [129] or monoclonal antibodies against recently involved cytokines such as IL22 [130], IL27 [131], IL37 [132], or angiotensin II [133], with more attention on hard outcomes of treatment such as the prevention of cardiovascular events [134]. New exciting evidence with putative treatment development includes immunosuppressive strategies via tolerance induction in autoreactive T cells [135] or targeting memory T cells using specific differentially expressed surface molecules or downstream signaling pathway proteins [136].

While biosimilars and comorbidities constitute new challenges [137–139], the rapid growth in our understanding of the pathogenesis of psoriasis and psoriatic arthritis over the past decade has been paralleled by the development of specific treatments which are not derived from RA or other rheumatological conditions, as supported by the different immunogenetic profiles [140] which also differentiates from other skin inflammatory [141, 142] or fibrotic [143] diseases. Indeed, a recent report suggested a common HLA susceptibility background for psoriasis and graft-versus-host disease [144]. Furthermore, psoriasis is now considered an autoimmune disease based on the identification of LL37 as an autoantigen for T cells [145] in patients with aggressive disease and the associated decrease of circulating CD4 + CXCR3+ T cells which in turn accumulate in the inflamed skin [146] or the role of MCAM (CD146) T cells [147]. T cells in psoriatic disease are indeed quite unique [145] and their production of IL17 represent a key to systemic [148] and skin [149] chronic inflammation and psoriatic articular manifestations [150] while new mechanisms for Th17 cells to influence the antimicrobial response were identified within IL26 [151] and the role of neutrophil extracellular traps (NET) awaits further definition [152]. Ultimately, psoriatic arthritis represents a paradigm for the spectrum of seronegative SpA and data on entheropatic SpA and their serological [153, 154] and immunogenetic [155–157] profiles or the ocular manifestations [158] support the urgent need for a multidisciplinary approach to autoimmune diseases as data on new treatments also converge on common mechanisms [159, 160].

Neuroimmunology

As in previous years, the field of neuroimmunology includes multiple sclerosis (MS) as the most prominent condition and this is reflected by the large number of articles in 2015, spanning from genetic and epigenetic disease susceptibility [161, 162] to biomarkers [163, 164] to potentially revolutionary treatments using helminths [165] or embryonic stem cells [166], among other reports [167–172]. From a pathogenic standpoint, a few reports were of major interest during the past year. First, there is growing attention on the mechanisms of antigen-specific B cells driving the central nervous system autoimmunity [173] via IFNbeta [174]. Second, IL17 role is rapidly gaining attention as represented by its involvement in optic nerve injury during MS [175–177] while new agents such as IL7 should also be considered [178]. Third, TNF receptor deficiency and the intestinal microbiota diversity concur to induce demyelinating diseases and support the search for host immune-microbiota-directed measures to prevent and treat CNS-demyelinating autoimmune disorders [179]. Fourth, there are now novel approaches to reinstate tolerance in MS and these are mostly based on promiscuous gene expression in medullary thymic epithelial cells [180]. Finally, the impact of Th and Treg cells in MS is better understood and will likely lead to new therapeutic avenues [181–186].

What to Expect in 2016

As in previous years, during 2015, common themes across autoimmune diseases significantly outnumbered differences and the former were particularly intriguing, as in the case of immunogenetic determinants [13, 16, 70, 124, 140, 155, 161, 187–191] on disease susceptibility, or the role of the microbiota [72, 179, 192, 193] on disease onset and progression or on treatment response which ultimately result in personalized medicine. Nonetheless, we feel that other reports from our literature search may prove key to future discoveries and we may foresee new developments to stem from rare disease paradigms or from cancer-like mechanisms while futuristic

treatments will likely become more established in specific subgroups of patients.

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