Clinical Reviews in Allergy & Immunology (2018) 55:239–253
https://doi.org/10.1007/s12016-018-8699-7

Autoimmunity in 2017

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Published online: 26 July 2018

Abstract
The number of peer-reviewed articles published during the 2017 solar year and retrieved using the "autoimmunity" key word increased significantly compared to 2016 while maintaining a stable share within the immunology field, following years with alternated fortunes. A detailed arbitrary analysis of the published articles in leading immunology and autoimmunity journals provides a privileged viewpoint on the current trends of research from both basic and clinical studies. Indeed, we are observing that major steps forward are found for rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis, among others. In particular, the new data on pregnancy success in lupus or biomarkers in systemic sclerosis are believed to change our management of these systemic conditions. In the case of rheumatoid arthritis, we have obtained data with significant implications in the understanding of the disease pathogenesis (as in the case of platelets), disease phenotyping, and new treatment options. Furthermore, the exponential growth of treatment options for cancer based on immune checkpoint modulation is paralleled by the need to address the potential autoimmunity side effects while taking advantage of new information obtained in paraneoplastic autoimmune conditions. Cumulatively, 2017 has been a very exciting year for autoimmune diseases, and we foresee that most of the data discussed herein will be followed by more extensive studies in the upcoming months.

Keywords Immune tolerance · Immune checkpoint inhibitors · Autoantibody · Platelet · Th17

2017 and Autoimmunity

As in previous 10 years, an overview of the publications dedicated to autoimmunity over the past solar year is now provided in this article. Indeed, 2017 was a very productive year with a 21% increase in the absolute number of publications compared to 2016, with 2944 papers retrieved on PubMed using "autoimmunity" as the search word (Fig. 1). This enormous increase may be associated with a global rise in immunology as the ratio of "autoimmunity" over "immunology" hits remained stable in 2017, with a 5% prevalence (− 0.1%) (Fig. 2).

To retrieve the most important publications regarding autoimmunity in 2017, we performed a literature research on PubMed in June 2018 among the major journals in the areas of immunology (*Nature Immunology*, *Journal of Immunology*, *Nature Medicine*, *Clinical Reviews in Allergy and Immunology*) and autoimmunity (*Autoimmunity Reviews*, *Journal of Autoimmunity*) and divided the articles in the most important clinical topics: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), and cancer and autoimmune diseases. Indeed, this approach led to an underrepresentation of other important diseases, such as diabetes [1–14], inflammatory myopathies and anti-synthetase syndrome [15–34], Sjogren's syndrome [35–42], vasculitis [43–69], and seronegative spondyloarthritidies, psoriatic disease, and related conditions [70–90]. Similarly, we overlooked papers on immunodeficiency [91–94] and autoimmune liver diseases [95–102], gender medicine [103–105], as well as studies regarding autoantibodies [106–117], which were otherwise well represented in 2017. Taken altogether, we should be aware that the choice of the articles to be briefly discussed is arbitrary and will lead to some missing references. Nonetheless, we will discuss the most recent findings regarding the new insights on pathogenesis of autoimmunity and more specifically of SLE, RA, SSc, and cancer association with autoimmune diseases.

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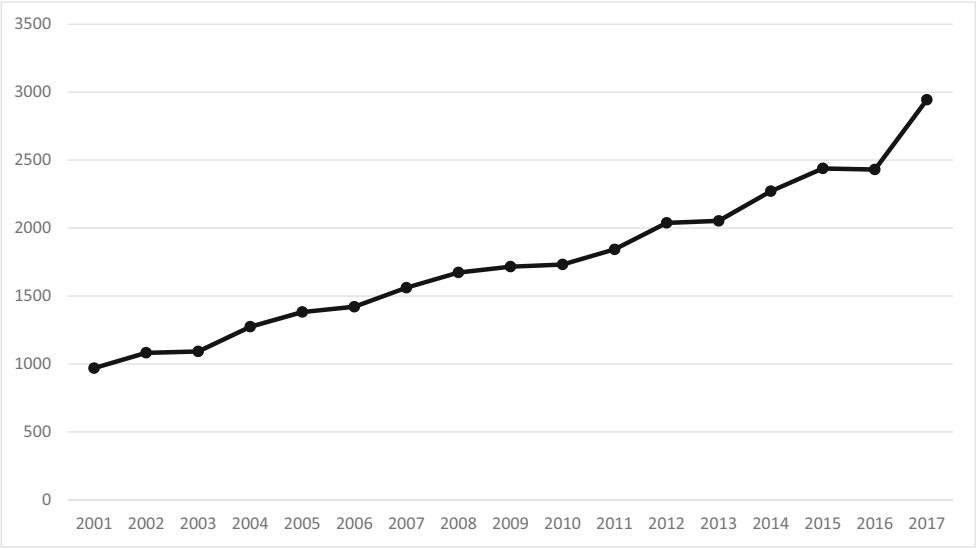

Fig. 1 Absolute number of articles retrieved in PubMed searching the word "autoimmunity" between 2001 and 2017

Getting Closer to the Mechanisms of Autoimmunity?

During the past year, several articles investigated novel mechanisms leading to autoimmunity [118–146], likely the most important knowledge gap and data have been provided on different cumulative hypotheses and specific cell types or genetic mechanisms.

The fascinating hypothesis based on the "nucleolus nexus" has been elegantly reviewed in 2017 and is based on chromatin disruption by nucleoli during cellular stress, when nucleoli can expand dramatically due to increased polyamine levels. Interestingly, an increase in polyamine levels has been reported in several autoimmune diseases. Moreover, the inactive X chromosome, a major epigenetic feature in female cells localized on the nuclear membrane, is in proximity with the nucleolus in up to 30% of cells throughout the cell cycle. In this view, the inactive X chromosome could abnormally interact with the nucleolus, which in turn will expand dramatically and engulf neighboring chromatin, leading to the disruption of the inactive X chromosome during cellular stress [147]. While the closeness with the inactive X chromosome is most suspect for autoimmune disease pathogenesis, other chromosomes could also be involved.

Other investigated mechanisms include small ubiquitin-like modifications (SUMOs) which are known to cause post-translational modifications that are crucial in activating protein functions. Through their interactions with innate immune

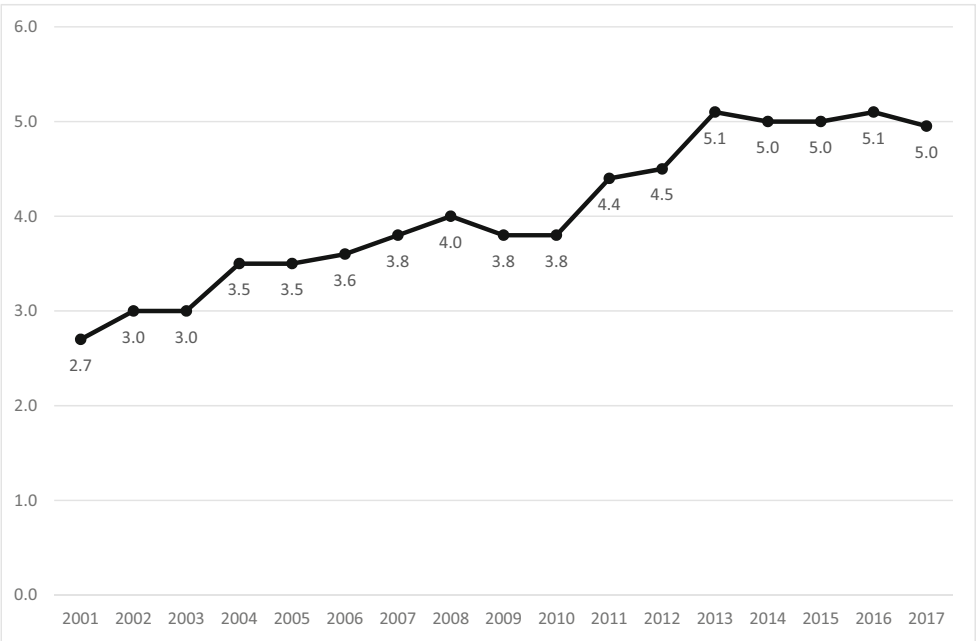

Fig. 2 Ratios of articles retrieved in PubMed searching the word "autoimmunity" vs "immunology" in 2001 through 2017

pathways, SUMOs promote an efficient immune response to pathogenetic challenge avoiding an excess of immune response that could lead to the development of autoimmune diseases. Environmental factors, i.e., bacteria and viruses, also interfere with the sumoylation of their own proteins and by interfering with sumoylation of host proteins, both leading to a decreased immune defense and increased infective potential [148]. SUMOs interact with various signaling pathways involved in innate immune response, in particular NF-κB and interferon (IFN), while are important in avoiding an excessive immune response and subsequent autoimmunity, as shown by the regulation of T regulatory cells (Treg) [149]. SUMO has been shown to play a role in several autoimmune diseases, including RA, Bechet's diseases, and type 1 diabetes (T1D) [148].

Third, long noncoding RNAs (lncRNAs), especially super-enhancer lncRNAs, are pervasive in autoimmune diseases, and their loci are in linkage with genome variants that confer a risk of autoimmunity, as it was reported by Aune et al. [150]. Interestingly, the transcriptional regulator Aire, which controls T cell tolerance by inducing the expression of a large repertoire of genes, has been shown to preferentially activate long chromatin stretchers, overloaded with transcriptional regulators, known as super-enhancers [151]. Additionally, topoisomerase 1 is a cardinal Aire partner, co-localizing on super-enhancers, and is required for the interaction of Aire with its associates [151].

Environmental factors are of great importance in the development of autoimmunity [152, 153], and the microbiome remains one of the most promising research areas, also because of the development of high-throughput sequencing, metagenome analysis, and other techniques. It is established that the microbiome influences the expression of Toll-like receptors (TLR) of antigen-presenting cells, and contributes to Th17/Treg imbalance. Moreover, it is well known that the gut microbiota and its metabolites can regulate immune cells and cytokines through epigenomic modifications, as short-chain fatty acids (SCFAs) promote the differentiation of naive T cells to Treg [154]. Recently, the salivary microbiota has been investigated in RA, and dysbiosis was found to be partially reversible after treatment [155]. The response to infections, tissue trauma, or inflammatory processes leads to the production of kinins, a group of potent autacoids that exert their action through two G-protein-coupled receptors, B1 and B2 receptors. Kinins have been involved in RA, multiple sclerosis (MS), T1D, and inflammatory bowel diseases (IBD) pathogenesis, and antagonists/agonists have emerged as new strategies for the treatment of autoimmunity with conflicting results [156].

Innate lymphoid cells (ILCs) have been recently defined as innate immune cells that function at mucosal tissue and organs, and secrete polarized cytokines and chemokines in rapid reaction to pathogens and infections, thereby contributing to the maintenance of homeostasis [157]. ILCs have been subdivided according to the type of cytokines produced: in group 1, similar to Th1 cells mainly producing IFN-gamma and TNF in response to IL-12 stimulation; group 2, similar to Th2 cells, producing IL-4, IL-5, IL-9, and IL-13; and group 3, similar to Th17 cells, producing IL-17 and IL-22. ILCs have also been found in association with several autoimmune diseases, in particular at early stages [157].

Endothelial cells, which are crucial mediators of SSc, show immunoregulatory properties and are involved in pathological angiogenesis, attraction of immune cells to sites of inflammation, and lymph node plasticity. The endothelium, in fact, actively participates to inflammation through antigen presentation, or through endothelial to mesenchymal transition [158]. All together, these findings suggest that targeting endothelial cells could contribute to control inflammation.

Besides, the endocrine system is in communication with the immune system and may influence the development of autoimmune diseases [159, 160]. Lines of evidence show that the development of autoimmune diseases is influenced by hormones, immunomodulators, and metabolic factors, such as vitamin D [161].

An important achievement of 2017 was the publication of a prospective study on the risk of developing autoimmune diseases after human papilloma virus (HPV) vaccination in France. The results of the present study show that there is no increased risk of developing any autoimmune condition after vaccination (adjusted odds ratio—OR 0.58, 95% confidence interval 0.41–0.83) in a 6-year follow-up [162].

Systemic Lupus Erythematosus

Articles on SLE were most relevant in the areas of disease pathogenesis, association with pregnancy, and medical treatment which will be reviewed separately.

Pathogenesis

While SLE is characterized mainly by B and T cell activation [163], also via IL-21 [164] and IL-23 [165], autoantibodies target multiple organ systems, resulting in chronic inflammation and organ damage, and the mechanisms underlying the dysregulation of the adaptive immune response remain enigmatic. Recent research on the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway revealed an aberrant expression in SLE. STAT proteins are major components of the IFN-dependent gene expression profile, and the STAT4 gene has been associated to SLE development in genome-wide association studies (GWAS). Moreover, increased levels of STAT1 have been described in SLE T and B cells, while STAT3 has a crucial role in Th17 differentiation, T follicular helper, and B cells [166].

Neutrophils in SLE are known to mediate tissue damage and act as a source of self-nucleic acids driving plasmacytoid dendritic cell activation and IFN production. As many as 20% of patients with SLE express autoantibodies to neutrophil-specific components, likely due to the formation of neutrophil extracellular traps (NETosis). However, recent evidence shows that neutrophils may acquire an immunosuppressive phenotype and restrain the development of autoreactivity in the early phases of the disease. A recent work by Bird et al. showed that in an animal model of SLE, neutrophils accumulate in secondary lymphoid organs over the course of SLE progression, localizing preferentially near T cells in the early phases of the disease and subsequently near B cells, while changing their transcriptional program from anti-inflammatory in early stages to activation in the late stages. These findings were confirmed by the observation that neutrophil depletion in the early SLE phases leads to disease progression, while in more advanced disease, it does not affect progression [167].

Variable endothelial dysfunction is frequently found in SLE patients, that express higher cardiovascular risk [168–170], and recent findings suggest that IFN-alpha promotes endothelial dysfunction through the suppression of the transcription and mRNA instability of endothelial NO synthase (eNOS) and upregulation of MCP1 and VCAM1 [171].

Pregnancy

While in the past years pregnancy was invariably discouraged in women with SLE due to severe consequences for both the mother and the child, the current evidence supports the view that having a successful pregnancy is possible in SLE. However, SLE still has a high impact on maternal and fetal outcomes, as demonstrated by a recent systematic literature review and meta-analysis including 529,778 women [172], and this major issue should warrant special care in dedicated clinics. In patients with lupus nephritis, pregnancy should be carefully planned during inactive stages, when pregnancy does not seem to increase the rate of SLE flares, worsen renal prognosis, or increase organ damage [173]. With regard to fetal outcomes, a recent systematic literature review suggests that maternal SLE is associated with learning disorders, specifically dyslexia, autism spectrum disorders, and speech problems; however, the included studies were assigned a low or moderate evidence level; therefore, prospective studies are needed to address this finding [174].

Therapy

While the treatment of other autoimmune diseases has dramatically changed in the last years, corticosteroids remain the cornerstone for the therapy of lupus nephritis, and repeated methyl-prednisolone pulses help reduce the dose of oral glucocorticoids and enhance clinical response [175], while biologic treatments remain of limited efficacy, especially in case of pre-existing organ damage and smoking [176]. Recommendations for the use of biologics have been published in 2017 to help define patients who require a biologic treatment, the type of biologic and co-treatment to use, how to evaluate treatment efficacy, and when to consider discontinuation (Table 1) [177]. Importantly, rituximab should be considered in those patients with refractory and corticosteroid-dependent forms of kidney or central nervous system involvement or severe autoimmune thrombocytopenia associated with SLE [178, 179], while belimumab is effective mainly in articular and skin manifestations [180], but could also be useful in lupus nephritis [181]. In the future, new B-cell-depleting drugs are expected to become available (Table 2): obinutuzumab, a novel anti-CD20 biologic, elicits a broader action compared to rituximab, and a randomized clinical trial (RCT) is currently ongoing. Furthermore, a vaccination with CD20-mimotope peptides in animal models of SLE led to a reduction in B cells and prolonged the survival in the treated mice [193].

After numerous failures, targeting IFN has gained some new interest with anifrolumab, targeting type I IFN receptor (IFNARI), which achieved promising results in non-nephritic SLE, and phase II–III studies are ongoing. In addition, it has been shown that patients expressing a higher IFN signature were less likely to respond to placebo, while response to anifrolumab was comparable [189]. Other biomarkers of organ involvement have been identified, and in the future, we may foresee that these will serve as prognostic markers in therapeutic decisions [194].

Preclinical data suggest new therapeutic avenues in the near future. In animal models, the inhibition of serine/threonine kinase IL-1R-associated kinase (IRAK) 4, a critical regulator of innate immunity, through BMS-986126, repressed cytokine production and suppressed skin inflammation, also in combination with prednisolone, suggesting a potential steroid sparing effect [195]. Hematopoietic stem cell transplantation (HSCT) has been proposed as a therapeutic option for SLE patients refractory to standard therapy, and a recent systematic literature review including 279 patients, of which 54 have secondary anti-phospholipid syndrome, showed promising results with an improvement after HSCT in disease activity and overall survival, with conversely more than 30% of patients suffering from infections, of which one resulted in the death of the patient [196]. Comorbidity prevention is crucial in SLE, osteoporosis and bone fractures remain the major causes of injury, and vitamin D levels are often reduced and should be supplemented with bisphosphonates to prevent glucocorticoid-induced osteoporosis [197].

Table 1 Recommendations for the use of biologics in systemic lupus erythematosus [177]

Which patients can benefit from the treatment with biologics?	
R1	With disease activity persistence, despite lupus conventional treatment or corticosteroid dependence (usual threshold ≥ 10 mg/day prednisone equivalent, dose discussed according to patient comorbidities and corticosteroid-related adverse events), actual patient adherence to treatment must be checked, before concluding treatment ineffectiveness, by clinical examination and by assessing, for example, blood levels of hydroxychloroquine.
R2	With active or corticosteroid-dependent lupus, despite hydroxychloroquine treatment and at least two successive immunosuppressive therapies (e.g., methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide), a biologic treatment can be prescribed.
R3	An anti-phospholipid syndrome (APS) associated with lupus is not an indication for treatment with biologics but can be discussed in case of the following: • Autoimmune thrombocytopenia (b25 G/l) associated with APS and/or hemorrhagic manifestations and refractory to usual treatments of immunological thrombocytopenia and/or a particular situation (surgery, bleeding requiring temporary discontinuation of anticoagulants, need to maintain platelet count ≥ 50 G/l because of sport or professional activity at risk of trauma). • Catastrophic APS (CAPS).
R4	A biologic treatment should not be used during pregnancy unless in an absolute medical necessity (disease activity threatening vital prognosis and/or compromising pregnancy continuation, despite lupus treatments authorized during pregnancy) after systemic consultation in a reference center for teratogenic agents to evaluate the safety of the proposed biologic.
R5	If a patient is exposed to a biologic treatment during pregnancy, a tight and specialized monitoring, including fetal echography, should be performed and the situation reported to a pharmacovigilance center and a reference center for teratogenic agents. The decision to stop a biologic should take into account disease activity, possibility of alternative treatments authorized during pregnancy, and type of biologic used.
What biologic treatment and co-treatment to use?	
R6	In refractory and corticosteroid-dependent disease forms (see definition in Recommendation 2), in the absence of kidney or central nervous system involvement or severe autoimmune thrombocytopenia, belimumab can be used.
R7	In refractory and corticosteroid-dependent forms of kidney or central nervous system involvement or severe autoimmune thrombocytopenia, rituximab can be used as the first biologic.
R8	A conventional immunosuppressant does not systematically need to be associated with a biologic.
R9	The combination of two immunomodulatory biologics is not indicated.
R10	In rhupus situations (rheumatoid arthritis and concomitant lupus), anti-TNF therapy, abatacept, rituximab, or tocilizumab can be used, keeping in mind the potential risk of lupus flare with anti-TNF agents and neutropenia with tocilizumab.
What information to give to patients	
R11	At the time of biologic initiation, clinicians should explain the reasons for the prescription, expected benefits, potential adverse events, monitoring modalities, and what to do in case of an adverse event, such as an infection. The need to discontinue a biologic before surgery should also be explained.
R12	Before initiating a biologic, clinicians should propose an update of vaccines according to current recommendations in the general population. If a live attenuated vaccine is required (e.g., yellow fever, rubella, mumps, and measles), the vaccine must be given at least 1 month before initiation of the biologic (live attenuated vaccines are contraindicated during biologic treatments). Hepatitis B and C serology should also be controlled. A hepatitis B pre-emptive anti-viral treatment should be discussed in case of nonseroconverted hepatitis B. It is highly recommended, before initiating a biologic treatment, to propose vaccination against pneumococcus and seasonal influenza. If a therapeutic emergency requires biological initiation before vaccination, nonlive vaccines may also be used, as soon as possible after biological initiation, although their effectiveness may be diminished.
R13	In women of childbearing age, effective contraception is required and must be prescribed for the whole treatment period. This contraception should be continued after biologic discontinuation for five half-lives of the biologic agent. If pregnancy is desired, it must be scheduled and treatments must be revised accordingly (see Recommendations 4 and 5).
How to judge the effectiveness of the biologic and when to stop treatment	
R14	The therapeutic goals in the 6 months after the initiation of a biologic treatment are as follows: • Decrease in disease activity, particularly regarding target organ(s), evaluated by a validated disease activity score and according to disease activity evaluated by the patient and the physician. • Oral corticosteroid discontinuation or corticosteroid-sparing (decrease ≥ 50% of the initial dose if the initial dose was N10 mg/day, to reach, if possible, a final dose ≤ 1 mg/10 kg prednisone equivalent).
R15	The monitoring of a biologic treatment should be clinical and based on laboratory examinations. Effectiveness should be assessed by validated disease activity scores. Tolerance should be assessed, with particular attention paid to the risk of infections. Safety should be assessed at each administration, both clinically and with laboratory examinations. With serious adverse events, the treatment should be stopped. According to the imputability of the adverse event to biologic treatment, the severity of the adverse event, its reversibility, the benefit/risk ratio for the patient, retreatment, or definitive discontinuation should be discussed.

Table 1 (continued)

R16	The safety and efficacy of a biologic treatment should be evaluated on a regular basis, at least at 1, 3, and 6 months after biologic initiation. In the absence of a documented clinical effectiveness at 6 months (see Recommendation 14), the biologic treatment should be discontinued.
R17	If a biologic treatment is maintained beyond 6 months, a re-evaluation (at least bi-annually) by a physician experienced in SLE management, possibly in conjunction with a reference center for systemic autoimmune diseases, should be performed to confirm its maintenance.

Rheumatoid Arthritis

Over the past solar year, research efforts on RA focused mostly on the fine mechanisms underlying disease development. From a genetic standpoint, single-nucleotide polymorphism (SNP) in the TRAF1 gene, a signaling adaptor known for TNF receptor-induced cell survival, is associated with RA, but also monocytes from non-RA subjects exhibiting this SNP show a reduction in TRAF1 protein and greater amounts of pro-inflammatory cytokine, suggesting a role in the increased inflammation [53]. Innate immunity plays a role in the early phases of RA, with TLR2 and TLR4 but also TLR5 and TLR7 capable to transform RA myeloid cells into M1 macrophages, which in collaboration with synovial fibroblasts secrete pro-inflammatory cytokines central to Th17 development [198]. Based on this growing amount of experimental evidence, novel approaches are being tested to target TLR function. Fibroblast-like synoviocytes from patients with RA express high levels of integrin alpha9 and its ligand, tenascin-C (Tn-C), and depletion of alpha9 suppresses the hyperplastic response of fibroblast-like synoviocytes and blunts the expression of MMP and IL-6 induced by TNF-alpha. B cells are crucial in RA pathogenesis, as shown also by the effectiveness of B-cell-depleting therapy and by numerous animal models. A new subset of memory B cell expressing Fc receptor like 4 (FcRL4) is enriched in RA joints and in the mucosa-associated lymphoid tissue. The FcRL4 + B cells, derived from the synovial fluid and tissue from patients with RA, manifest a larger proportion of recombinant antibodies and reactivity toward citrullinated autoantigens and an increased usage of the IgA isotype. These cells have been shown to produce high levels of RANKL, which could contribute in turn to the joint destruction and erosions observed in RA [199]. On the other hand, B regulatory cells (Breg) producing IL-10 play an important role in initiating and maintaining chronic inflammation in autoimmune diseases, such as RA. Breg are both numerically and functionally impaired in RA [200] and can convert into RANKL-producing cells, partially induced by TNF-alpha, thus impairing their immunosuppressive functions and exacerbating disease progression. These cells quantitatively correlate with RA disease activity and inversely with the number of Breg producing IL-10. Of note,

Table 2 Novel therapies for systemic lupus erythematosus

Therapeutic agent	Target	Phase	Findings	References
B cells				
Atacicept	Human recombinant fusion protein inhibiting BLyS/APRIL	II–III	Effective in patients with high disease activity and serologically active	[182–184]
Blisibimod	High affinity fusion protein BLyS antagonist	III	Primary endpoint not met, but reduction in proteinuria and biomarker responses	[182, 185]
Tabalumab	Human anti-BLyS monoclonal antibody	II–III	Efficacy in reducing flares, autoantibodies, complement and B cells	[182, 186, 187]
Ocrelizumab	Humanized anti-CD20 monoclonal antibody	III	Did not meet the primary endpoint	[188]
Obinutuzumab	Humanized anti-CD20 monoclonal antibody	II	Trial ongoing	[189–191]
Epratuzumab	Humanized anti-CD22 monoclonal antibody	II	Did not meet primary endpoint	[182]
Interferon pathway				
Anifrolumab	Human anti-type I IFN receptor monoclonal antibody	II–III	Effective	[182]
Rontalizumab	Humanized anti-IFN-alpha monoclonal antibody	II–III	Did not meet primary endpoint	[182]
Sifalimumab	Fully human anti-IFN-alpha monoclonal antibody	II–III	Did not meet primary endpoint	[182]
Other drugs				
Baricitinib	JAK1/2 inhibitor	II–III	Effective	[192]

RANKL-producing Bregs can promote osteoclast differentiation, which does not occur in healthy individuals [201].

Platelets are least known players that can modulate the immune response of leukocytes, particularly T cells, with a reduction of the proliferation and production of IFN-gamma and IL-17. This could have therapeutic potential, and Zamora et al. demonstrated that co-cultured platelets and lymphocytes lead to a reduction in the production of IFN-gamma and TNF-alpha, T cell proliferation, and the expression of CD25, PD-L1, and SLAM, while increasing CD39. The co-culture of platelets and RA synovial fluid cells reduces the inflammatory cytokines and increases IL-10 production [202].

Environmental factors are well known to contribute to RA pathogenesis, and smoking represents the major risk factor for the development of RA with serum anti-citrullinated peptide antibodies. A novel mechanism by which the tobacco habit may contribute to RA implies that smoking activates also CD8+ T cells, and causes the release of survivin [203]. Vitamin D, as for other autoimmune diseases [161], has a relationship with disease activity and patient-reported outcomes in RA [204] and could also play a role as a tolerogenic adjuvant in a model of RA [205].

Clinical research in RA is currently focused on biomarkers predicting the therapeutic response since up to 40% of patients with RA will discontinue drugs because of inefficacy or adverse events [206]; in this view, it has been reported that response to anti-TNF-alpha treatment is associated with high levels of GM-CSF and GM-CSF + T cells, while nonresponders are characterized by higher IL-17 levels, suggesting that RA not responding to anti-TNF is likely to be driven by different inflammatory pathways [207], and this is also suggested by the report that the response to abatacept, a fusion protein CTLA4-Ig, is associated with the levels of CD38 + CD27+ memory B cells [47, 208]. NETosis could also act as biomarker for therapeutic effectiveness in RA as it is increased in RA, and correlates with disease activity and autoantibodies positivity, while treatment with anti-TNF and IL-6 receptor inhibitor decreases the generation of NETs, in correlation with a reduction in disease activity and inflammatory markers [209].

Novel therapeutic targets in RA include, quite unexpectedly, risingly the programmed cell death-1 (PD-1) pathway which is currently central to cancer immunotherapy. In fact, PD-1 + T cells accumulate in RA synovial fluid, and PD-1 knockout animals develop inflammatory arthritis [210]. However, targeting PD-1 in cancer immunotherapy may induce autoimmune manifestations resembling RA, and further research is needed before a modulation of PD-1 in RA can be carried forward. Recent studies have demonstrated the anti-inflammatory properties of bee venom, a conglomeration of allergens, toxins, and other triggers of the immune response. In alternative medicine, bee venom has been used to retrieve pain with promising results, but more controlled trials are needed to determine the immune reaction with cells in the context of inflammation [211].

Systemic Sclerosis

SSc is a rare systemic disease characterized by the classical triad of immune system activation, vasculopathy, and altered collagen deposition resulting in widespread fibrosis [212–214] for which there is a large therapeutic unmet need. In the last year, an increasing body of literature is focusing on the identification of genetic and epigenetic markers of SSc, as well as the identification of biomarkers for the various disease manifestations and organ involvement [215].

Different from other autoimmune and chronic inflammatory diseases, various studies have supported the notion that genetic susceptibility is of modest importance in SSc, also supported by the low concordance in monozygotic twins. The strongest genetic association for SSc lies in the MHC region, with loci in the HLA-DRB1, HLA-DQB1, HLA-DPB1, and HLA-DOA1. Non-HLA genes associated with SSc include genes for B and T cell activation and innate immunity, while others are involved in extracellular matrix deposition, cytokines, and autophagy. Among these, STAT4 has the strongest association with SSc, but in addition to genetics, environmental factors, in particular exposure to heavy metals [216], have been shown to contribute to the development of SSc. Extensive epigenetic changes have been described in SSc, in particular regarding DNA methylation, histone modification, and dysregulated noncoding RNA levels, contributing to fibrosis, immune dysregulation, and impaired angiogenesis [217], while suggesting the possibility of therapeutic interventions to reprogram the epigenomic landscape.

The role of Tregs has also been investigated in SSc as it is known that Tregs have a decreased functional capacity, while they might be increased in number, especially in active SSc, possibly representing a failed regulatory attempt of the immune system. Conversely, in long-standing SSc, Treg frequency is reduced both in the peripheral blood and in the skin. Furthermore, it has been shown that Tregs may participate also in the inflammatory process as well as in transformation induced by the microenvironment in pathogenic T effector cells, with a Th2 or Th17 phenotype with pro-fibrotic and pro-inflammatory activity [218]. In this view, the evaluation of Tregs could represent possible future biomarkers for disease activity.

SSc is almost invariably associated with serum autoantibodies, especially anti-nuclear antibodies (ANA), but novel autoantibodies functionally active against cell-surface receptors have been identified and could have a possible pathogenetic link with the disease clinical manifestations. In particular, antibodies directed against the PDGF receptor have been shown to induce fibrosis in SSc animal models, fibrillin-1-directed antibodies have been found in SSc sera, while a number of antibodies directed toward the TGF-beta signaling pathway and to heterogeneous nuclear ribonucleoprotein A1 and superoxide dismutase 2 which protects against ROS have also been observed and could be linked all together to the fibrotic phenotype of SSc. In

the search for clinical phenotype prediction, antibodies directed against the muscarinic acetylcholine (ACh) receptors have been linked to gastrointestinal dysfunction. Antibodies to endothelial cells (AECAs) have been identified in 86% of SSc sera and are associated with more severe disease, organ involvement, and pulmonary arterial hypertension, as well as with vascular and perivascular involvement and digital ulceration. AECAs are believed to have a role in the modulation of endothelial cell function and survival in SSc [212]. Finally, antibodies to angiotensin/endothelin receptors are present in 70% of SSc sera, with limited specificity for SSc, and are associated with a more severe disease and death. Cumulatively, these functional autoantibodies could act both as biomarkers and be responsible for specific disease manifestations and may further be investigated as therapeutic targets [219]. In this view, intravenous immunoglobulins (IVIGs) exhibit immunomodulatory and anti-fibrotic properties and are relevant in the treatment of musculoskeletal involvement, systemic inflammation, and digestive tract symptoms stemming from SSc [220, 221].

Cancer and Autoimmunity

The association between cancer and autoimmunity has been long suspected and then demonstrated in clinical and basic research, while recently published data from large registries and databases have changed our perspective on the association of most autoimmune diseases and cancer, as well as the presumed association with anti-TNF therapy. Meanwhile, the association between Sjögren syndrome and B cell lymphoma, especially MALT lymphoma, is well established and an early diagnosis is facilitated to identify patients at high risk by biomarkers, i.e., BAFF and beta2-microglobulin, and clinical manifestations such as parotid gland enlargement, purpura, lymphadenopathy, glomerulonephritis, peripheral neuropathy, or splenomegaly [222]. In the case of SSc, the positivity for anti-RNA polymerase III or Pm/Scl antibodies is associated with a paraneoplastic disease, particularly breast and lung cancer [223, 224]. The association of polymyositis/dermatomyositis with cancer is also well recognized, in particular for anti-TIF1-gamma antibody-positive subjects [222, 225].

Conversely, with the advent of effective immune checkpoint inhibitors for cancer, the resulting immunotoxicity and autoimmunity have been advocated as the Achilles heel of this revolutionary treatment [226]. These drugs have transformed the treatment for certain tumors, by blocking interactions that normally suppress T cell responses, i.e., CTLA4 and PD-1/PD-L1. However, these alterations in the adaptive immune response may lead to the development of forms of arthritis and other autoimmune manifestations, and the mechanisms have not been elucidated yet. In the future, we may speculate that checkpoint-based immunotherapy will be developed also for autoimmune diseases [227].

What to Expect in 2018

As in previous years, during 2017, common themes across autoimmune diseases significantly outnumbered differences and this supports the view that the several remaining unanswered questions in autoimmune diseases will be derived by research in unrelated areas. Indeed, common grounds include innate immunity, microbiota as a link to environmental factors, and shared treatment approaches. While we are excited by the significant increase in the number of publications that appeared in 2017 compared to the previous year, the quality of the research also continues to grow and more elegant solutions are expected to be reported in different areas.

Compliance with Ethical Standards

Conflict of Interest The author declares that he has no conflict of interest.

Ethical Approval and Informed Consent The present article is a review; thus, no informed consent was obtained.

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