

Autoimmunity in 2012

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Abstract The initiation and perpetuation of autoimmunity recognize numerous checkpoints, from the genomic susceptibility to the breakdown of tolerance. This latter phenomenon includes the loss of B cell anergy and T regulatory cell failure, as well as the production of autoantibodies and autoreactive T cells. These mechanisms ultimately lead to tissue injury via different mechanisms that span from the production of proinflammatory cytokines to the chemotaxis of immune cells to the target sites. The pathways to autoimmunity have been widely investigated over the past year and resulted in a number of articles in peer-reviewed journals that has increased by nearly 10 % compared to 2011. We herein follow on the attempt to provide a brief discussion of the majority of articles on autoimmune diseases that were published in the major immunology journals in the previous solar year. The selection is necessarily arbitrary and may thus not be seen as comprehensive but reflects current research trends. Indeed, 2012 articles were mostly dedicated to define new and old mechanisms with potential therapeutic implications in autoimmunity in general, though based on specific clinical conditions or animal models. As paradigmatic examples, the environmental influence on autoimmunity, Th17 changes modulating the autoimmune response, serum autoantibodies and B cell changes as biomarkers and therapeutic targets were major issues addressed by experimental articles in 2012. Further, a growing number of studies investigated the sex bias of autoimmunity and supported different working hypotheses to explain the female predominance, including sex chromosome changes and reproductive life factors. In conclusion, the resulting scenario illustrates that common factors may underlie different autoimmune diseases and this is well represented by

the observed alterations in interferon- α and TGF β or by the shared signaling pathways.

Keywords Immune tolerance · Vitamin D · Th17 · IL12 · Connective tissue disease

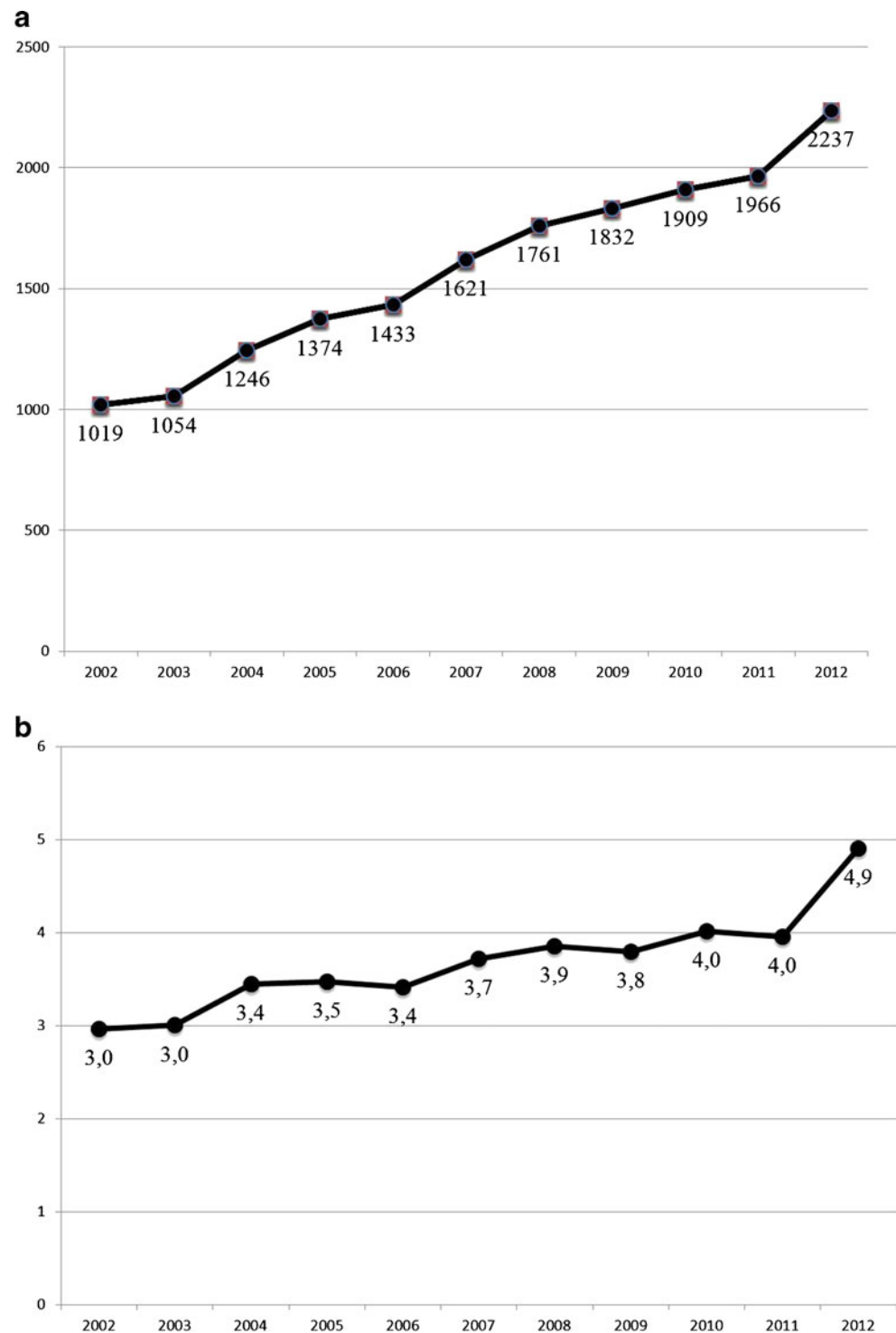
Autoimmunity Research Becomes of Age

Our effort to monitor the publications appearing in a solar year in the major immunology journals is rapidly becoming a regular appointment for researchers interested in autoimmune diseases to provide a brief discussion of current and future trends in the wide field of autoimmunity. The PubMed search retrieved 2,237 articles in English published in 2012 utilizing “autoimmunity” as the key word and this represents a surprising 9 % increase from the previous year ($n=1966$). Previous comparisons demonstrated steady yearly increases but figures were significantly lower in the 3–4 % range (Fig. 1, panel A). Of note, we also utilized a similar approach to identify articles in English published in 2012 in the broader area of “immunology” and retrieved 45,585 papers with a significant reduction (–9 %, approximately 4000 items) compared to previous years. Indeed, the proportion of articles involved in autoimmunity grew significantly and now represents nearly one in 20 immunology papers (Fig. 1, panel B). Of note, specific autoimmune or chronic inflammatory conditions represented significantly different proportions of published articles over the year (Fig. 2). As in previous years [1] we performed a preliminary search using the “autoimmunity” keyword within the major journals in the immunology (*Journal of Immunology*, *Nature Immunology*, *Nature Medicine*, *Clinical Reviews in Allergy and Immunology*) and autoimmunity (*Autoimmunity*, *Autoimmunity Reviews*, *Journal of Autoimmunity*). Of note, all these journals increased their impact factors according to the Thompson/Reuters Journal Citation Report 2011 Edition. A further screening of the several hundred publications retrieved from the journals led to the identification of articles including more specific key words that constitute the titles of subsequent paragraphs.

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Fig. 1 Full articles in English published during 2012 and previous years were retrieved from PubMed using the search word “autoimmunity”. The yearly trends in absolute numbers (panel a) and as ratio within publications retrieved using “immunology” (panel b) are represented



Genetics, Epigenetics, and Environmental Factors

The role of genetics in determining the susceptibility to autoimmune diseases remains largely enigmatic despite the strenuous efforts reported in recent years with the plethora of genome-wide association studies in most complex diseases [2, 3] and this is possibly related to the wide clinical variability

of most conditions [4, 5] or the numerous intercurrent factors as well represented by vaccines [6]. These GWAS, nevertheless, have provided incomplete information on the individual factors leading to disease onset and most identified polymorphisms were found in a minority of patients thus making their testing of little use in clinical practice. Conversely, GWAS may provide solid candidates for mechanistic studies, as represented by

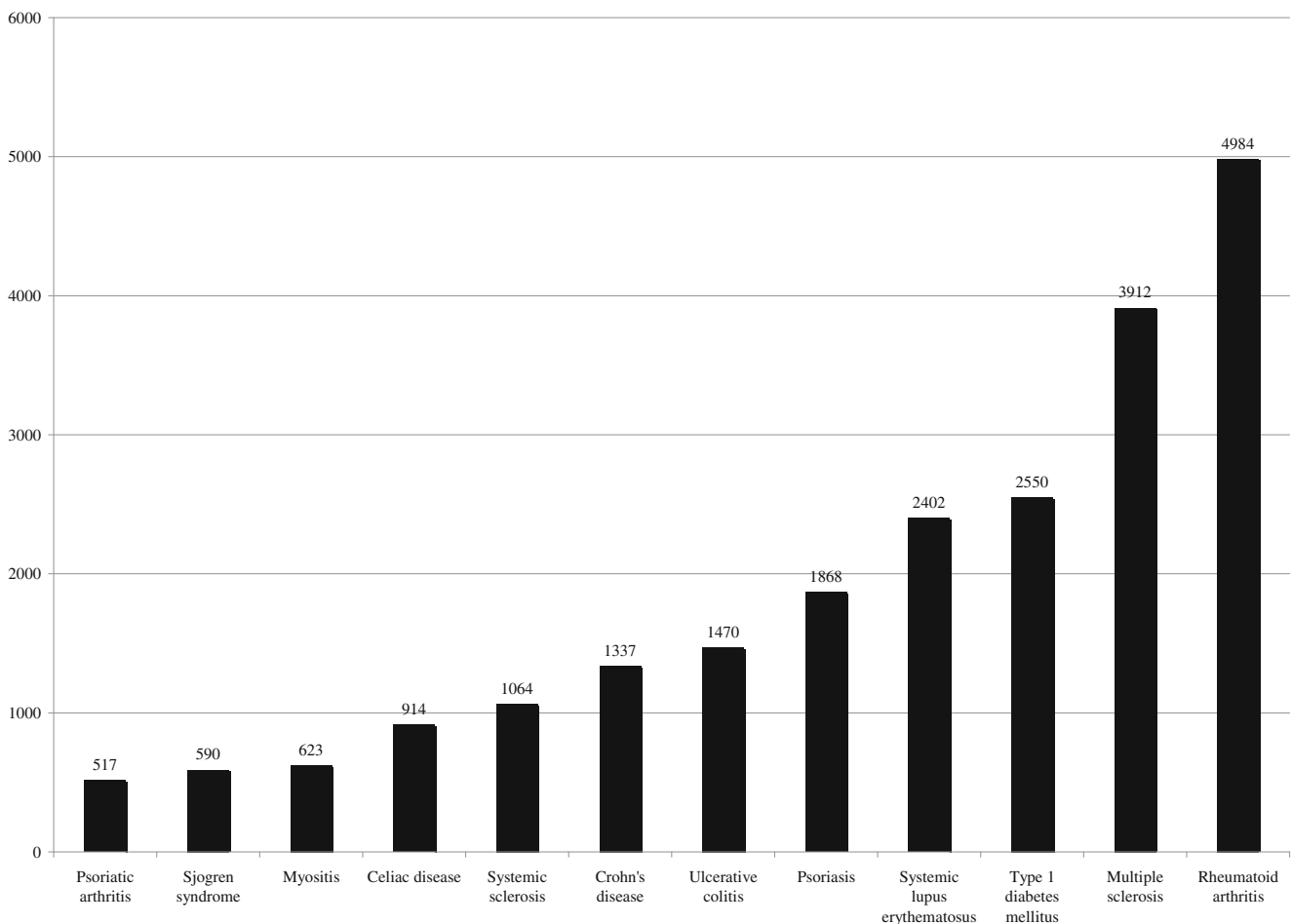


Fig. 2 Full articles in English published during 2012 were retrieved from PubMed for specific autoimmune and chronic inflammatory conditions. Absolute numbers are sorted and represented

endoplasmic reticulum aminopeptidases ERAP1 and ERAP2 as shared genetic factors in multiple conditions such as ankylosing spondylitis, psoriasis, and multiple sclerosis [7] or the polymorphisms of PTPN22 altering T and B cell functions in type 1 diabetes [8] as well as in other diseases [9]. The study of connective tissues disease has been recently discussed in a comprehensive review that encouraged the expansion of the available GWAS data to subgroups of patients or comorbid conditions such as Sjogren syndrome [10]. In a complementary fashion, there is an optimal model for the study of complex diseases and this is represented by monozygotic twins manifesting discordant clinical phenotypes. The available data on concordance rates in autoimmune diseases were reviewed by Bogdanos and colleagues [11] to demonstrate that genomic factors are not sufficient for disease initiation while next-generation sequencing may identify rare variants in these unique sets of patients and controls. The scenario is even more complex as specific alleles are demonstrated to influence the functional features of immune cell subpopulations, as in the case of NK and autoimmunity [12]. Complementary to the role of genetics and of environmental factors, epigenetics appear to be of major importance in determining the onset of autoimmune

diseases and may explain the discrepancy of clinical phenotypes between monozygotic twins. During 2012, two review articles have comprehensively discussed the role of epigenetics, particularly DNA methylation, in the pathogenesis of autoimmunity and hematological malignancy [13], possibly via effector memory T regulatory cell changes [14], and in identifying new potential treatments for autoimmunity [15]. Of note, epigenetics was also discussed as a major mechanism linking autoimmunity to the environment [16]. An experimental work presented in 2012 illustrated the role of changes in the methylation of the FoxP3 gene in the paradigmatic IPEX syndrome [17] and may suggest new pathways also for other female-predominant autoimmune diseases [18] in which X and Y chromosome abnormalities have been reported [19–21]. FoxP3, furthermore, was recently demonstrated to be crucial for the maintenance of privileged tissues such as the eye with retina-specific mechanisms [22] and may prove an ideal target for specific conditions such as orchitis [23] or autoimmune hepatitis [24], a condition in which the metalloproteinase balance may be skewed in liver lymphocytes [25]. Furthermore, new evidence suggests that histone code changes may mediate the influence of viral infections on autoimmune diseases [26], possibly through the

modulation of MHC molecule expression in antigen-presenting cells [27] but we should encourage mechanistic studies to better define the role of viruses in autoimmunity which may be mediated by immunity pathways [28], possibly acting on marginal zone B cells [29], TNF α mechanisms via oncoprotein LMP1 [30], or immediate early proteins [27]. Recent experimental evidence suggests that type 1 interferons may modulate the resistance to viral infections and autoimmunity [31], as recently demonstrated by an elegant work in a murine model of autoimmune hemolytic anemia to which IL2 and dendritic cells are crucial via Th1 cytokines [32], while interferon gamma may be crucial to xenobiotic-induced autoimmune manifestations [33]. Interferon regulatory factor 4 has been further proposed as a common therapeutic target in different chronic inflammatory and autoimmune diseases [34]. The impact of environmental factors in autoimmune diseases has been the subject of a series of articles published in 2012 following an expert panel workshop sponsored by the National Institute of Environmental Health Science in 2010 [2] to address common questions by patients and relatives [35]. The workshop led to the publication of new proposed criteria for environmentally induced autoimmunity [36] which are expected to clarify the numerous proposed associations and reducing the claims related to specific pollutants in causing connective tissue diseases or other autoimmune manifestations. On the other hand, the workshop also produced herculean efforts to define the putative mechanisms [16], epidemiological evidence [37], and animal models [38] supporting the role of specific environmental factors in determining autoimmunity. In the case of animal models, the authors support the importance of the genetic background and clearly identify highest degrees of confidence for a causative link between mercury, pristane, and specific infections with autoimmunity [38] while STAT6 is an ideal example of genetic predisposition to murine autoimmune diseases [39]. In the case of infectious agents, we expect that the wide panel of agents that can be studied in multi-platform approaches (coined the “infectome”) may contribute to clarify this fascinating hypothesis [40]. The study of epidemiology data, on the other hand, allows to determine whether a latitudinal gradient or geographical clusters exist for autoimmune diseases [37, 41]. Further, pathogenetic mechanisms of different types have been identified to link environmental factors and autoimmunity and are well represented by molecular mimicry following infections, antigen modifications, and adjuvant effects [16]. A recent report in Kawasaki disease stressed the importance of the coexistence of genomic (in this case the ITPKC polymorphism) and environmental factors (thimerosal) to produce oxidative stress and contribute to disease susceptibility [42]. One representative example is provided by the aryl hydrocarbon receptor that is modulated by xenobiotics to modulate allergy and chronic inflammation through an enhanced production of IL17 by mast cells [43]. Further, nutrients are ideal examples of environmental factors modulating the autoimmune injury and reduced

levels of vitamin D are possibly the most widely studied candidates in their capacity to trigger the breakdown of tolerance and to cause a more aggressive disease [44] while polyphenols found in green tea and cocoa may modulate the autoimmune injury of salivary glands in Sjogren’s syndrome [45], a multifactorial condition [46, 47] in which protein modifications such as ubiquitination may be a crucial step [48]. The digestive system appears to be pivotal in mediating the environmental influence on autoimmunity [49] through different mechanisms including iron absorption and the subsequent polarization of macrophages to the M1 or M2 phenotype [50] which may prove a promising target to restore an effective apoptotic cell clearance [51] that appears defective in murine lupus and other models [52], possibly via the contribution of neutrophil extracellular traps released by dying granulocytes [53]. Finally, we note that environmental sex hormones may also contribute to the female predominance of the majority of autoimmune diseases [54], along with age-related factors such as telomerase activity or specific inflammatory pathways [55]. As autoimmunity incidence increases with age a recent report of single-cell network profiling demonstrated that specific immune cell subpopulations undergo different changes with aging thus possibly explaining the immunosenescence causing higher infection rates [56].

Sex and Autoimmunity

The striking female predominance observed in the majority of diseases remains one of the most enigmatic issues in our understanding of autoimmunity [57], as supported also by the different phenotypes in spontaneous and induced animal models of autoimmune disease [58], including graft-versus-host disease [59], and viral infection [60]. It could be argued that the established sex ratios may in turn perpetuate the physician tendency to underdiagnose autoimmune diseases in men and a recent comprehensive review of social and economic factors related to sex and autoimmunity may support the importance of such stereotypes [61]. To this regard, it is of note that patients with female-predominant autoimmune disease such as lupus are at risk for male-prevalent heart disease and that this appears to be immune-mediated [62] with putative immunization strategies being developed [63]. Over the past year, several authors addressed the questions on sex and autoimmunity, particularly following the 8th International Congress of Autoimmunity that took place in Granada in May 2012 [64]. Among the proposed mechanisms, we first note that the most obvious hypotheses include different environmental exposures, particularly cosmetics [18], sex chromosome [19] and other sex-related genomic factors [9], as demonstrated by the natural model of women with Turner’s syndrome [65] or premature ovarian failure [66]. Further, we are intrigued by the observations that longevity may manifest different patterns in female and male sex through different

signaling pathways [55] and that elevated prolactin levels may correlate with lupus manifestations, particularly serositis [67] and interfere with B cell tolerance in systemic and tissue-specific diseases [68]. B cells and plasma cells are crucial to autoimmune diseases and attacking their niches is a promising approach to complex conditions, beyond depletion [69], also in consideration of their role in autoreactivity to heterologous protein challenge [70]. Nevertheless, prolactin is only one of the sex hormones that may be involved in the frequent reproductive abnormalities in men and women with autoimmune diseases [71, 72]. As an example, estrogens manifest numerous immunomodulatory effects and are produced also by unsuspected cells such as the synovocytes in rheumatoid arthritis [73], one of the most paradigmatic female-predominant autoimmune diseases [74]. In this clinical setting, furthermore, B cell function is also modulated by sex hormones in the production of autoantibodies [75]. Finally, T regulatory cells from women with type 1 diabetes produced significantly lower levels of TGF β but maintained a similar functional capacity compared to cells from male patients [76].

Autoantibodies, B Cells

While new scenarios are discovered [77], the independent role of old [78] and new [79] serum autoantibodies, B cells [80–82], and plasma cells [69, 70] in autoimmune diseases has been largely established over the decades and the past 12 months confirmed this view with numerous lines of evidence [16] with significant overlapping with infectious diseases such as chronic hepatitis B [83] or HIV [84]. In the case of antibodies, one should be aware that there is a fine balance between the pathogenetic and physiological roles of immunoglobulins, as well represented by natural antibodies in type 1 diabetes [85] and lupus nephritis [86], or autoimmune polyendocrine syndromes [87]. Importantly, antibodies constitute a major part of acquired immunity with strict interconnections with the innate compartment, as illustrated by the toll-like receptor dependent production of pathogenetic autoantibodies in lupus models [88, 89] or the regulation of autoreactive plasma cells by plasmacytoid dendritic cells [90] and macrophages [91]. One paradigmatic condition appears to be bullous skin disease [92, 93] in which autoantibody profiles are being developed [94] along with the identification of putative mechanisms for clinical comorbidities [95] and novel evidence on the role of NK cells [96] in the unique B cell homing observed in the skin [97]. Growing data point towards the importance of Fc receptors [98] and complement proteins [99] in the perpetuation of the autoantibody-mediated injury and local B1 cell survival via BAFF signaling [100]; to this regard, the hydrolysis of IgG may provide a new therapeutic approach for the autoreactivity directed at type 2 collagen in rheumatoid arthritis [101] and Mincle is a C-type lectin receptor that may regulate B cell response [102]. Furthermore, there are now

technological tools that allow to determine the autoantibody proteomes, as recently demonstrated for anti-Ro52 antibodies in Sjogren syndrome [103], a condition in which memory B cells appear to be quantitatively reduced in target organs [104] and B cell depletion is effective [105]. In the same condition, Bombardieri and colleagues reported the induction of murine disease using a replication-deficient adenovirus [106]. The role of T cells in determining B cell tolerance or activation has been largely investigated over the past year and data support the importance of a unique subset of CD4⁺ cells [107], the absence of CD59 [108] and the presence of IL21 receptor [109] in lupus-prone mice, BCR signaling on T3 B cells [110] and negative B cell regulation [111], and high levels of IL21 in graft-versus-host disease [112] in regulating autoantibody production via different mechanisms including BAFF [113]. In a complementary fashion, plasma cells are pivotal to the frequently observed resistance to steroids in autoimmune diseases and the bone marrow is the site for such memory plasma cells in lupus-prone mice [114] and its microenvironment induces B cell apoptosis while inhibiting B cell proliferation [115]. Finally, we expect that further data are produced on the importance of IL10 in the B cell maturation process and autoimmunity onset [116, 117], particularly in the B10 regulatory subpopulation [118].

Cytokines, T Regulatory, and Th17 Cells

Cytokines remain the major messengers that mediate the fine balance between inflammatory stimuli, autoimmunity, and tolerance and this is well illustrated in rheumatoid arthritis and the available cytokine-targeting treatments [74] which are currently only hypothesized for lupus [119]. We may also expect that anti-cytokine vaccines will rapidly become an effective option but data are currently limited [120]. Of note, targeting TNF α in autoimmune diseases also triggers novel autoimmune manifestations, particularly in terms of antinuclear (ANA) and anti dsDNA antibodies [121] while growing evidence is being produced on the key role of IL2 [32, 122–124], IL10 [116, 118, 125, 126], and IL21 [109, 112] in tolerance and autoimmunity. A specific mention should be warranted for IL6 which has been recently the center of numerous studies and is a promising therapeutic targets in the prevention and treatment of autoimmunity [43, 74, 91, 102, 126–128]. Finally, we should not overlook the effects of additional homeostatic factors such as prostaglandin E2 on virtually all immune cell populations, including Th17 and T regulatory cells [129].

Similar to 2011 [130–168], the study of Th17 and T regulatory cells has been a major issue in the field of autoimmunity and studies have included genomic associations with functional consequences [169], disease modulation in experimental arthritis [170], EBV involvement in multiple sclerosis models [171], and the identification of ubc13 and SLAM as a new mechanisms inducing Th17 differentiation in lupus [172, 173]. Conversely, IL17A has been found to act on both

neutrophil chemotaxis and endothelial activation thus linking two major mechanisms observed in chronic inflammation [174] and myeloid suppressors cells influence Th1 and Th17 cells in multiple sclerosis [175]. In general terms, there is increasing data supporting the possibility of targeting Th17 cells in the treatment of autoimmune diseases [176] but results are conflicting [177] and mechanisms of periodontal infections may further complicate the resulting scenario [128]. The Th17 scenario has become significantly more complex over the past year with the demonstration of a significant role of the Ikaros transcription factor Aiolos with an IL2-dependent mechanism [124], the ubiquitin-specific protease USP25 via TRAF5 and TRAF6 [178], the heterochromatin component TRIM28 via an altered expression of TGF β and other cytokines [179], and the dopamine receptor D5 expressed by dendritic cells [180]. The field of T regulatory cells has also witnessed some seminal contribution over the past year and this cell population is continuing to represent a key to tolerance, particularly after the resolution of an effective immune response [181, 182] and fascinating opportunities for cell programming from precursor cells [183], modulating the apoptosis features [184], or modify T cell receptor specificities [185] are being discovered. Several studies have now pointed towards TGF β as a pivotal cytokine for the functional balance of T regulatory cells [76, 186] while IL10 and IL2 may also contribute to such balance via B cells acting on the glucocorticoid-induced TNFR ligand [117] and STAT5a phosphorylation [122] or the ICOS pathway [123], respectively. Among their numerous functional features, T regulatory cells maintain self antigen tolerance in the presence of viral infections of the central nervous system [187], are crucial to the helminth-mediated protection from autoimmune disease [188], and may be modulated by fasting via leptin levels in lupus [189].

Specific Autoimmune Diseases

The majority of data presented in the previous chapters were gathered from animal models or patients with specific autoimmune diseases but transcend the clinical setting in which they were obtained; conversely, other studies were more focused on specific conditions (namely systemic lupus erythematosus, Sjogren syndrome, scleroderma, rheumatoid arthritis, type 1 diabetes, and multiple sclerosis) and will be discussed in this chapter.

The pathogenetic mechanisms of systemic lupus erythematosus and scleroderma remain largely enigmatic [190] despite the numerous animal models available and the large amount of experimental data obtained in this disease, as previously discussed for T regulatory and Th17 cells or in the case of sex differences [9, 58, 64]. New potential treatment approaches for lupus to complement old ones [191] are suggested by experimental data on apoptotic blebs [52] and the possibility that macrophage polarization may restore the

apoptotic clearance [51] and neutrophil extracellular traps [53], STAT6 modulation in atopy [39], and interferon alpha impact on B cell selection [192]. More importantly, we are intrigued by the possibility of treating lupus with the induction of peptide tolerance in T regulatory cells [193] or delivering immunomodulatory molecules using peptides such as the 21-mer peptide P140 [194]. Further, data on the importance of innate immunity in general [89] and toll-like receptor in particular are being produced in experimental studies and may translate into effective therapeutic approaches [88], along with new cytokine profiles such as IL21 [109, 112] or IL10 [116], and kinase inhibitors [195]. We are convinced that the major innate immunity dysfunctions observed in pediatric autoimmunity [196] and autoinflammation [197] may provide a good paradigm for new research directions, as illustrated by genomic studies [198] or recent data on the ribonucleoproteins on the NLRP3 inflammasome [199]. One of the most challenging clinical features of lupus remains the reproductive impairment with altered sex hormone profiles and the frequent infertility [71], pregnancy complications [200, 201], or the effects of menopause [202]. In the former case, recent data support the importance of prolactin levels in determining the manifestations of lupus [68], particularly in terms of serositis [67].

In the case of Sjogren's syndrome [46, 47], the most recent data from 2012 support the importance of Ro52 autoantibody clonotypes [103] and other mechanisms [104, 106, 203] in this paradigmatic epithelial disease [204] in which clinical manifestations may vary significantly to include smell disturbances and peripheral neuropathy [5, 205].

Limited data have been reported for scleroderma in 2012. First, a specific DAMP signal is reported to be associated with platelet activation thus concurring to the vascular injury associated with the disease [206]. Second, scleroderma is one of the autoimmune diseases in which a significant association with anti-*Toxoplasma gondii* antibodies has been reported, along with antiphospholipid syndrome, autoimmune thyroid disease, and rheumatoid arthritis [207]. Third, the enhanced frequency of X monosomy in peripheral blood lymphocytes from women with scleroderma was recapitulated several years after our original report and may thus confirm the role of sex chromosomes in disease susceptibility [208], particularly following menopause [202].

Rheumatoid arthritis is a systemic autoimmune condition characterized by the positivity for highly specific serum autoantibodies and a dramatic response to anti-TNF α and B cell depleting treatments [74]. As such, rheumatoid arthritis represents the ideal condition in which basic and clinical evidence must be sought at the same time to provide a comprehensive understanding [209]. Similar to most autoimmune disease, women largely outnumber men among cases of rheumatoid arthritis and one fascinating hypothesis is based on the different B cell response to HLA class II [75] with possible functional

implications on the effector cells [80, 81] that may accumulate in lymph nodes draining the inflamed joints expressing CD23, CD21, and CD1d markers [210]. Further, putative therapeutic approaches have been proposed and include the use of an HSP-60 derived peptide which was proven effective in two models of arthritis [211], anti-cytokine vaccination [120], or the modulation of NK cell function [212]. In terms of etiology, we note that two articles followed different experimental approaches to suggest that *T. gondii* [207] and Epstein–Barr virus [213] may contribute to the onset of rheumatoid arthritis.

Type 1 diabetes is a unique autoimmune disease characterized by a male predominance, a high tissue-specificity, and the lack of effective immunosuppressive treatments. As discussed in previous sections, data on type 1 diabetes have been obtained from numerous studies over the past year. Indeed, specific immune dysfunctions were reported, including the observation that Gr1⁺ CD11b⁺ cells may suppress the disease-inducing activity of CD4⁺ and CD8⁺ T cells thus delaying the onset of experimental diabetes [214]. Further, T regulatory cells are impaired in patients and experimental models via the ICOS pathway [123, 215] thus providing an ideal target for individualized cellular treatment [122], along with the induction of pancreatic overexpression of CD40 [216]. Of note, all these changes require a permissive genomic background that remains to be defined, particularly for interferon genes [217].

The immune bases of multiple sclerosis have been largely investigated [218, 219] and promising data have been reported, as represented by T cell apoptosis [220] and by the suggestion that neurofilament release may be a biomarker for disease staging [221]. As an example, a murine model of multiple sclerosis has been reported in T cell receptor transgenic animals and manifest significant CD4⁺ and CD8⁺ cells contributing to the clinical phenotype [222], possibly via different expression profiles of the IL7RA pathway [223] or microRNA 29ab1 [224].

Conclusions and Hopes for the Current Year

We are convinced that 2012 provided an enormous amount of novel findings to the field of autoimmunity and are intrigued by the possibilities that may be uncovered by the reported data. Nevertheless, we encourage a common effort to answer the questions remaining on the etiology and putative treatments for multiple autoimmune diseases [225], particularly if coexisting [226] with the possibility of common genomic bases [227]. First, research should determine whether common immunological pathways may be important to multiple conditions, as well represented by vitamin D supplementation data in preventing or modulating autoimmunity [44, 228]. Second, pathway analyses and next-generation sequencing data should be visualized in terms of autoimmunity in general and may provide common targets for new therapies [229]. Third, the study of the general population [41] and unique

monozygotic twins [11] are ideal tools to determine the importance of genetic, environmental, and epigenetic factors in the susceptibility to autoimmune diseases. As a result, we may assume that any year of research will bring us closer to discriminate the future of autoimmunity [230].

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