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Editorial

Advances in the pathogenesis and treatment of autoimmunity

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Autoimmune diseases are one of the major health problems worldwide, with a greater disease burden in industrialized countries. Type 1 diabetes (T1D), rheumatoid arthritis (RA), and multiple sclerosis (MS) are examples of such diseases. A concerted effort by basic scientists and physicians in both academic and industry settings over the past decade or so has resulted in significant advances in our efforts to meet the challenges posed by autoimmune diseases. These advances pertain to a better understanding of the disease processes in autoimmunity as well as novel approaches for the treatment of these diseases. In this special issue, "*Advances in Autoimmunity*," leading experts have shared their research work and perspectives on these developments along with future projections. A synopsis of 8 articles is presented here under four sub-sections.

1. The role of antigen-presenting cells (APCs), including B cells, in the pathogenesis of autoimmunity, and approaches to target them for therapeutic purposes

Lees [1] has outlined various therapeutic approaches for autoimmunity by describing conventional T cell-intrinsic targets and then focusing on novel approaches targeting APCs as well as interfering with particular steps in the pathways involved in the presentation of antigens to the T cells. A comprehensive background offers insights into antigen presentation as a risk factor for autoimmunity; into the evidence for antigen presentation as a critical requirement for ongoing autoimmunity; into the impact of current therapeutic approaches on antigen presentation; and into the antigen-specific targeting of APCs. Furthermore, interesting examples from patients with autoimmunity and the corresponding animal models supporting the above information are discussed. These diseases include T1D, experimental thyroiditis, RA, and MS/experimental autoimmune encephalomyelitis (EAE). The targeting of tissue-specific antigens displayed by APCs for the treatment of autoimmunity is a promising approach of increasing interest. However, it is imperative that any potential interference with homeostatic regulatory responses that depend on effective antigen processing and presentation is taken into consideration and avoided, as much as possible.

Forsthuber and colleagues [2] have emphasized upon the role of B cells in the immunopathogenesis of MS, which has conventionally been considered to be a predominantly T cell-mediated autoimmune disease. This article presents the rationale for the pathogenic role of B cells in autoimmunity, in part stemming from the success of B cell-depletion therapy in MS. Insightful description is provided for the intricacies of B cell tolerance; for the role of B cells in the pathogenesis of MS (including antibody-dependent/independent mechanisms, and protective B cell functions); for B cell-depleting therapies (e.g., Rituximab); for revisiting the effects of earlier disease-modifying therapies on B cells (e.g., interferon-β and Glatiramer acetate); and for other strategies that remain to be fully explored (e.g., targeting plasmablasts and plasma cells, B cell survival factors, granulocyte-macrophage colony-stimulating factor (GM-CSF), and B cell signaling pathways; and inducing IL-10-producing regulatory B cells). However, several challenges regarding variations in disease outcomes in B cell-targeted therapies remain to be overcome. For example, the inability of the therapeutic antibody to reach pathogenic B cell populations at the diseased site, the depletion of beneficial regulatory B cell populations, and the genetic

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polymorphisms that affect antibody-mediated cytotoxicity.

2. The pathogenic versus immunomodulatory roles of adenosine, IL-17, T helper 17 (Th17) cells, and B cells

Sun's group [3] has elaborated upon the role of activated γδ T cells in the enhancement of Th17-type responses in a murine model of experimental autoimmune uveitis (EAU). This effect involves extracellular adenosine, which not only serves as an 'alarm' or danger signal, but also has an immunosuppressive effect on αβ T cells. Activated γδ T cells express increased level of adenosine receptor A2 (A2AR), which avidly binds adenosine, but express reduced levels of CD73 (a glycosyl phosphatidylinositol-linked membrane protein), which generates adenosine from adenosine monophosphate. The preferential binding of adenosine by γδ T cells preempts its binding to, and signaling in, αβ T cells. This, combined with decreased adenosine generation, leads to reduced suppressive effect of adenosine on the effector Th17 cells, thereby enhancing the severity of EAU. It is proposed that the stimulatory effects of adenosine on Th17 cells, while sparing Th1 cells might be attributable to the differential expression of various AR receptors, their affinities for binding to adenosine, and downstream signaling pathways triggered in these two subsets of T cells. Thus, this article has highlighted one of the mechanisms involving adenosine for the regulation of Th17 response in autoimmunity by activated γδ T cells.

Singh et al. [4] have described novel regulatory Th17 (Treg17) cells as well as regulatory B cells (Breg) that control pathogenic immune responses in T1D and other autoimmune diseases. CD4+ regulatory T cells are comprised of Forkhead Box P3 (Foxp3)$^+$ T regulatory (Treg) cells and Foxp3$^-$ T regulatory cells. The latter include Th2, Th3, and type 1 regulatory cells (Tr1) cells. These cells control the activity of pathogenic effector Th17 cells, which produce the cytokines IL-17 and IL-22 (high), and express the transcription factor RAR-related orphan receptor gamma (RORγt). Unlike the pathogenic Th17 that are differentiated in the presence of IL-23 and IL-6, the Treg17 cells are produced when T cells differentiate under the influence of TGF-β and IL-23, and they secrete IL-17, IL-10, and IL-22 (low) along with the expression of aryl hydrocarbon receptor (AhR). The inhibition of pathogenic Th17 by Treg17 involves STAT3 and IL-10 signaling. In contrast to Treg subsets, the precise lineage and phenotype of Breg is not yet clear. However, several studies have revealed their inhibitory effect via IL-10 and other immunomodulatory cytokines (IL-35 and TGF-β). In addition, B cells can amplify the regulatory process by inducing Treg cells.

Hamad's group [5] has presented an overview of the role of IL-17 in the pathogenesis of several autoimmune diseases, including T1D, MS, psoriasis (Ps), psoriatic arthritis (PsA), RA, systemic lupus erythematosus (SLE), Hashimoto's thyroiditis (HT), inflammatory bowel disease (IBD), and celiac disease (CD). The authors have also summarized the current status of multiple clinical trials using IL-17-neutralizing/blocking therapies that have either been completed or are in progress, as well as those already approved for clinical use. The latter include IL-17-based approaches for the treatment of Ps, PsA, plaque Ps, and CD. However, in certain clinical situations such as IBD, the IL-17-based therapy might either be ineffective or even worsen the outcome. Furthermore, the utility of this approach in another autoimmune disease, T1D, remains to be fully determined. It is hoped that in the near future, the testing of second-generation products and improving their therapeutic index would enhance the outcomes and expand the clinical application of IL-17 therapy to other autoimmune diseases besides those mentioned above. Thus, this article provides critical insights into the pathogenic role of IL-17 in autoimmunity as well as the success versus limitation of therapies targeting IL-17.

3. The role of Treg cells in the induction of self-tolerance and the treatment of autoimmunity

Prabhakar and colleagues [6] have reviewed basic aspects of central and peripheral tolerance, with special emphasis on the generation and mode of action of Foxp3$^+$ Treg (Treg) in the thymus (tTreg) and in the periphery (piTreg); on the utility of adoptive Treg cellular therapy for the control of autoimmunity; on the lack of easy-to-use methods for the isolation and expansion of Treg; and on the high costs associated with the preparation of clinical-grade Treg for infusion into patients. This review has highlighted the instability of subsets of Treg, which can lose Foxp3 (exFoxp3 Treg) and acquire pro-inflammatory and pathogenic attributes under certain conditions. It is clear that Treg can exhibit different levels of heterogeneity under normal versus autoimmune conditions. Furthermore, tTreg differ from piTreg; piTreg show differences when compared with tissue-resident Treg; and the in vivo generated piTreg differ from in vitro generated piTreg. In regard to Foxp3, it can help distinguish murine Treg from activated/effector T cells, but it is not a reliable marker for this distinction in the corresponding human T cell subsets. Also, Foxp3 alone is insufficient for optimal Treg function. Additional mediators such as CD25 (IL-2Rα), cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), glucocorticoid-induced TNFR-related protein (GITR), and Eos (a transcription factor) contribute to the suppressive activity of Treg.

4. Modulation of autoimmunity by the host microbiome and other environmental factors

Taneja et al. [7] have addressed the role of the intestinal microbiome in the maintenance of the innate and adaptive components of host immunity as well as the impact of an imbalanced microbiome (dysbiosis) on the pathogenesis of autoimmunity. The microbiome of patients with autoimmunity (e.g., T1D, RA, or MS) may display distinct aberrations when comparing one autoimmune disease with another. Furthermore, the microbes produce certain metabolites (e.g., short chain fatty acids (SCFAs)) that interact with the host immune system, and can influence the differentiation and/or activity of defined T cell subsets. The unique features of the microbiome in T1D along with the role of butyrate in the disease process are highlighted in this article. However, this association with butyrate needs to be validated through clinical trials. Various factors affecting the microbiome composition in MS have been described, but a direct cause-and-effect relationship with microbiota remains to be established. Observations in RA and animal models have suggested the abundance of certain rare bacterial lineages (e.g., Collinsella) that show association with disease susceptibility and severity. Also described herein are various ways to modulate dysbiosis in autoimmune diseases, for example, by the use of probiotics.

Moudgil's group [8] has described the role of environmental factors in the pathogenesis of autoimmunity, and elaborated upon "Hygiene hypothesis" to explain the inverse relationship between exposure to certain environmental microbes, helminths, and defined antigens, and the development and progression of autoimmunity. The effect of such exposure was protective in nature in most conditions examined. The Hygiene hypothesis was originally proposed to explain the effect of environmental factors on hay fever and other allergies, but later expanded in its scope to cover helminthic infections, microbiota, and autoimmune diseases. In this article, examples of autoimmune disease models in which the housing environment has a significant effect on the severity of autoimmunity, and the underlying mechanisms effecting these outcomes are described. Also discussed is the role of commensal microbiota and the metabolites (e.g., SCFA and tryptophan catabolites), produced either by specific microbial species de novo or via their action on particular dietary products, in host immunity and autoimmune pathogenesis. These metabolites include ligands for AhR. Furthermore, various approaches to rectify the dysbiosis in RA are described, as also emphasized in the article by Taneja and colleagues.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cellimm.2019.04.005.

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