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GUEST EDITORIAL

Biomarkers and Pathogenic Mechanisms in Autoimmunity

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Introduction

The overall frequency of all autoimmune diseases in the general population is estimated at 5–8 %. More importantly, there has been an alarming increase in incidence for autoimmune diseases in recent decades. All ages are affected with onset from childhood to late adulthood. Persons of all racial, ethnic, and socioeconomic groups are affected, although the impact of racial background varies in different autoimmune diseases. In respect of this and the growing interest in autoimmune diseases, the 10th International Congress on Autoimmunity was held in the historical and beautiful city, Leipzig, Germany, on April 2016. This meeting as all previous ones was organized by Prof. Yehuda Shoenfeld and was attended by almost 1000 participants from all over the world. Aspects of autoimmune and auto-inflammatory diseases were discussed, and fruitful collaborations between scientists were initiated. In this special issue of Immunological Research, we chose to report on some of the developments in diagnostic issues and biomarkers in the field of autoimmune diseases. In addition, many sessions were dedicated to mechanisms and therapeutic aspects of autoimmune diseases.

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Autoantibodies/Biomarkers in Various Autoimmune Diseases

Specific autoantibodies are important in defining accurate diagnosis and in guiding clinicians when differential diagnosis is required. However, many autoantibodies are becoming good biomarkers in the process of choosing proper therapy and in predicting the course of many diseases [1, 2]. In this respect, data were presented aiming to compare different assays for detecting anti-mitochondrial autoantibodies, two indirect immunofluorescence assays using HEp-2 cell lines and the multiplexed line-blot assay and EliA-M2 commercially available for patients with primary biliary cirrhosis. They show that both the qualitative EUROLINE and the quantitative EliA-M2 assays are of high diagnostic accuracy for primary biliary cirrhosis, with specificity higher than the immunofluorescence method. Their additional data suggested the advantage of using EliA-M2 for diagnostic purposes but also for monitoring disease activity [3].

The choice of treatment regimen in patients with rheumatoid arthritis (RA) is largely depends on trial and error. Aiming to predict a patient's response to methotrexate or other therapies, a novel theranostic marker was presented. Serological antigen selection (SAS), a high-throughput technique that uses cDNA phage display, was used to identify novel antigen targets. Here, it was suggested that cDNA phage display library is of great potential for the discovery of novel theranostic autoantibody biomarkers which could predict the above-needed therapeutic response [4]. The issue of specific autoantibodies

was presented by showing that parietal cell antibody to gastric H/K ATPase is of high diagnostic value for the diagnosis of autoimmune gastritis. In this report, the above-discussed parietal cell antibody was found to be highly predictive for the development of pernicious anemia [5]. The issue of using specific autoantibodies in defining various clinical aspects of primary Sjögren's syndrome was also presented. Useful biomarkers were suggested being able to predict the development of lymphoma. Additional biomarkers were discussed as useful tools for the early diagnosis, prognosis, and response to treatment [6]. Positive anti-citrullinated peptide antibody (ACPA) is considered highly specific in the diagnosis of rheumatoid arthritis, but is also useful for early diagnosis and for predicting response to therapy. In this meeting, a new colloidal gold lateral-flow point-of-care kit for the detection of ACPA was compared to other conventional assays. The objective was to show that CCPoint assay is a novel technology that allows for a rapid accurate analysis of ACPA during the patient's visit in the rheumatology office [7].

The Better Detection of Antinuclear Antibodies

Commercially available HEp-2 ANA readers are widely used for detecting antinuclear antibodies. In a "real-life" study, the comparison of computer-aided diagnosis (CAD) systems from three different vendors (Zenit G-sight, Helios, and NOVA view) was compared to indirect immunofluorescence (IFA) readings of ANA slides by two to three expert physicians. When 261 consecutive samples with suspected autoimmune diseases were tested for ANA, CAD systems were proven to represent one of the most important novel elements of harmonization in the autoimmunity field, reducing intra- and inter-laboratory variability in a new vision of the diagnostic autoimmune platform [8]. In another study, automated IFA methods were compared with established manual IFA screening. In this study, 120 ANA-positive sera from patients with autoimmune disease and 78 ANA-negative sera from patients without autoimmune disease were assessed using the two of CAD systems (Helios and NOVA view). Excellent correlations between the two systems were reported [9]. The development of the International Consensus of ANA Patterns (ICAP) will contribute to the whole concept of developing a consensus nomenclature between laboratories in describing different IFA patterns [10].

Autoantibody Mechanisms of Action

Many autoimmune diseases have been described presenting antibodies targeting specific tissue antigens; yet, the most are associated with the presence of autoantibodies with multiple specificities. Irregular antibodies are produced by alloimmunization because of pregnancies or blood transfusions. They are called "irregular" due to target erythrocyte antigens from "rare blood systems," those different from the ABO system. In a presented study, the authors show that these antibodies are widely investigated in immunohematology since their presence in blood donors may lead to difficulties in blood typing and in blood cross-matching, or to induce hemolytic transfusion reactions. They also show that these antibodies do not induce hemolysis in vitro but enhance macrophage-mediated phagocytosis of erythrocytes [11]. Idiopathic hypertrophic pachymeningitis (IHP), characterized by the thickening of cerebral or spinal dura mater, is considered to be of inflammatory origin. A subset of IHP is now considered IgG4-related sclerosing disease, and therefore, IgG4 should be analyzed when cerebral symptoms are present. Although the pathological process in IHP remains unclear, the treatment often includes glucocorticoid together with other immunosuppressive agents and non-responsive cases may be treated with rituximab [12]. To address the type of autoantibodies potentially involved in coagulation and in the CNS involvement in antiphospholipid syndrome (APS), a new mouse model of APS was studied. The authors described the existence of anti-Annexin A2 (ANXA2) antibodies in the brain of mice induced by immunization of β2-glycoprotein I (GPI). This study suggests an immune response to the β2-GPI–ANXA2 complex and provides a novel ANXA2 immunization model which will serve to study the role these antibodies in APS [13].

Immune-Mediated Diseases and Mechanisms of Inflammation

The immune system continuously faces internal and external influences; however, even when it is compromised or overwhelmed, it will still endeavor to regain and maintain tolerance to self. To promote this, a modified vaccination technique was presented in this meeting, described as the third vaccination method. It has two components: purified exogenous/endogenous antigens and a high-titer-specific antibody against the target antigen. This vaccination technique can be used both prophylactically and therapeutically by mimicking the immune system's natural abilities [14]. The issue of switching patients suffering from spondyloarthritis from innovator infliximab to biosimilar therapy was also discussed in this meeting. Patients from three rheumatology centers were switched to biosimilar infliximab and followed during 6 months. Biosimilars were found to be as effective as the innovator ones and with similar efficacy, and with no adverse events or the development of antidrug antibody [15]. Among the

many immune-mediated diseases, the following were presented in different sessions. Pulmonary hyalinizing granuloma (PHG) was reviewed from a total of 80 articles in the literature. PHG is a rare and benign disease mimicking lung neoplasm and is frequently associated with inflammatory systemic disorders. Frequently, ANA is positive and was found in 22 % of cases, as well as the involvement of pro-inflammatory cytokines [16]. In another discussed issue, the increased level of serum ferritin and of the bone remodeling marker osteoprotegerin were suggested to be independent predictors of hip fracture in postmenopausal women hospitalized for fragility fracture. These data were based on the assessment of 49 postmenopausal patients with non-traumatic hip fracture when compared with 66 osteoporotic women without a history of hip fracture [17]. Finally, 282 cases of biopsy-proven leukocytoclastic vasculitis were discussed with a focus on direct immunofluorescence detection of immunoglobulin and complement deposition at the blood vessel wall. Their findings support immune complex deposition in the blood vessel wall being relevant to determine underlying conditions related to this disease [18, 19]. The meeting ended up with many clinical and basic issues being discussed and with a clear agreement that the 11th meeting on autoimmunity should be a wider platform for new issues to be raised, and move on toward further scientific achievements.

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