Immunologic Research (2018) 66:633–636
https://doi.org/10.1007/s12026-019-09071-1

GUEST EDITORIAL

Editorial: autoimmunity—the ever endless world

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Published online: 1 March 2019

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Editorial

The field of autoimmunity and autoimmune diseases is continuously growing. New clinical aspects, diagnostic approaches, and advanced therapeutic tools are introduced in the clinic turning this field richer and colorful. In this respect, the international meetings on updates in autoimmunity organized periodically by Prof Y. Shoenfeld are widely attended by physicians, scientists, and young fellows in the field. The recent meeting in Lisbon 2018 was attended by almost 2000 participants, having the opportunity to listen and talk to many leaders in the fields of autoimmune and auto-inflammatory diseases. All participants were able to discuss and plan various collaborations, being the basis of future studies. In this issue of Immunologic Research, readers will be able to taste some of the important flavors of this meeting.

1. *Special aspects in autoimmune diseases:* Clinical and radiological features of sarcoidosis and tuberculosis are frequently overlapping, raising in many cases diagnostic dilemmas. In a study by Strashinova et al., significant differences were found by demonstrating specific immune complexes allowing a better diagnosis of sarcoidosis or tuberculosis. The approval of definite sarcoidosis is crucial in order to prevent over-diagnosis of tuberculosis [1, 2]. The definition of vertigo and progressive hearing loss as being immune-mediated or of autoimmune origin is considered especially when other relevant symptoms are present. In a study by Russo et al., the authors suggest to pay attention when hearing loss is progressive and vertigo is associated with abnormal immune responses. The sooner steroid therapy is initiated, the higher the chances of recovery from inner ear damages [3, 4]. In a study by Sharif et al., a big population-based cross-sectional study of patients with hypothyroidism was compared with age-matched and sex frequency–matched controls. The proportion of schizophrenia in hypothyroidism patients was significantly higher than in controls (2.01% vs 1.25% $p < 0.0001$) [5]. Looking for biomarkers and risk factors for future rheumatoid arthritis (RA), Kalinkovich et al. summarizes data supporting the view that the transition from the at-risk stage to clinical RA is governed by a link between autoimmunity, inflammation, and dysbiosis [6]. In another study by Lambert et al., the authors evaluated the development of antibodies against dietary aquaporins (corn, soybean, spinach, and others) and their potential cross-reactivity with brain aquaporins leading to blood–brain barrier permeability and the development of neuro-autoimmunity [7]. The role of regulatory mechanisms in the pathogenesis of psoriasis is widely investigated. T regulatory cells (Tregs) are required for normal skin homeostasis and the prevention of skin immune-mediated diseases; therefore, the status of Tregs and other regulatory molecules in the skin of psoriatic patients is important. In this respect, the study by Sabag et al. show for the first time the downregulation of IL-10 and Tregs in correlation with increased pro-inflammatory cytokines. In addition to this, regulatory markers of Tregs such as semaphorin3A and neuropilin-1 were also downregulated in the skin of these patients, suggesting semaphorin3A to be a therapeutic tool in psoriasis [8, 9]. In this issue of Immune Research, the contribution of immune-mediated

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responses, cytokines, and chemokines is reported to play role in the pathogenesis of papillary thyroid cancer [10]. In another study, IL-1 and organochlorine pesticides (OCP) are assessed in respect to their contribution to puberty disorders [11]. The "X chromosome-nucleolus" hypothesis is reviewed by Brooks WH., where he provides a comprehensive explanation of how autoantibodies can develop following cellular stress. The hypothesis connects autoimmune diseases with the impact of environmental factors, such as viruses, through epigenetic disruption [12].

2. *ASIA syndrome and related issues:* The use of vaccines has proven to be highly effective in controlling and eradicating infectious diseases. However, vaccines can occasionally induce harmful immune responses recognized recently as the autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA syndrome) [13, 14]. Aspects of ASIA are reviewed in this issue by Asin et al. suggesting that vaccines might cause over-immunization through repetitive vaccinations along a defined period of time or by the use of several vaccine doses in as single time point [15]. Adverse effects following human papilloma virus vaccination were reported in many case reports from many countries. These were mainly neuropsychiatric, cardiovascular, and immune-mediated diseases such as multiple sclerosis and others. The frequency and whether these side effects are vaccine-related remain controversial [16]. Neuropsychiatric adverse effects following HPV vaccination was reported in many Japanese girls leading at some point to withdrawing the recommendation for HPV vaccination by the Japanese Ministry of Public Health, Labor, and Welfare. In a study by Ikeda et al., the authors could not demonstrate a causal link between HPV vaccination and the development of the above mentioned adverse effects. The study shows that the period of HPV vaccination considerably overlapped with that of unique post-vaccination symptom development, adding that new patients with possible HPV vaccine–related symptoms have not appeared during 28-month follow-up period [17]. In another study by Blitshetyn et al., the authors review case series from several countries in which symptom clusters following HPV vaccination are described. These include headache, disabling fatigue, widespread pain, limb weakness, and others. The article proposes that vaccine-triggered immune-mediated autonomic dysfunction could lead to the development of de novo post-HPV vaccination syndrome possibly in genetically susceptible individuals [18]. The usage of immune systems' natural abilities aiming to correct abnormal immune responses support the development of modified vaccination techniques (MVT) proved to be correct immunological misshapes. This was reviewed by Barabas et al. [19].
3. *Diagnostic tools in autoimmune diseases:* In a report by Roggenbuck et al., the authors describe a new method for a reliable detection of TSH-receptor (TSHR) antibodies. A third-generation ELISA was shown to be of higher sensitivity and specificity in detecting these antibodies when compared to other methods of detection [20]. The study by Ogric et al. established the importance of monitoring serum concentrations of infliximab (IFX) and adalimumab (ADL) and the levels of their antibodies in patients with inflammatory diseases. This may help clinicians to better adjust dose, increase safety, and effectiveness of treatment [21]. In this regard, the authors evaluated and validated a new in-house ELISA for IFX and ADL, together with anti-IFX and anti-ADL ELISAs for routine detection and further analysis with acid dissociation of immune complexes [22]. Nazarov et al. analyzed the concentration of immunoglobulin free light chains (FLCs) in cerebrospinal fluid in 92 patients with multiple sclerosis to find that increased levels of intrathecal production of FLCs may become a good prognostic biomarker for MS disease severity. Increased levels may predict increased frequency of brain atrophy in MS [23]. Recent studies have demonstrated that micro-particles (MPs) have a role in intracellular communication. In the review by Barbati et al., the authors hypothesize that increased MPs play role in the pathogenesis of autoimmune diseases such as RA. They also suggest that MPs may have a role in endothelial dysfunction, contributing to atherosclerosis in RA [24, 25]. The study by Takasawa et al. was performed to assess the expression of human REG family genes in IBD patients. REG1α and REG1β and REGIV genes were found to be overexpressed in patients with ulcerative colitis and Crohns' disease, suggesting them to be good biomarkers for a better diagnosis [26]. In a work by Dreyfus et al., immunoglobulin G response to EBV-encoded proteins which share regions with human immune response proteins was characterized. They suggest that proteomic "molecular fingerprints" is potentially useful in early diagnosis and monitoring of autoantibody production and response to therapy in EBV-related autoimmune syndromes [27].
4. *Therapeutic regimens in autoimmune diseases:* Intravenous immunoglobulin (IVIg) therapy is reported to be beneficial in many studies, by preventing inflammation in a wide range of autoimmune diseases. In a recent study, this beneficial effect was assessed in a French nationwide cohort of 46 patients with systemic sclerosis [28]; however, and though rare, side effects of IVIg such as thrombotic events or severe headaches should be considered. In this respect, the temporal association between a series of thromboembolic events and IVIg therapy in patients with rheumatic diseases is reviewed in this issue by Lidar M. In this review, nine patients who had suffered a thromboembolic event within a week after receiving an IVIg infusion are described in details [29]. Therapeutic interventions aiming at improving spasticity in MS were

mentioned in many studies. In one of these, immunologic pathway and autoimmune-mediated neuronal damage in MS is reviewed, in addition to pharmacological modulation of spasticity and therapeutic interventions [30]. In contribution to this, the efficacy of immune reconstitution therapy (IRT) in MS is reviewed by Karussis, providing a novel concept for MS therapy with substantial advances over chronic immunosuppressive therapy. IRT therapies have shown a significantly higher level of efficacy in MS. The "Holy grail" of treatment of autoimmunity, which is to re-induce the disrupted self-tolerance, seems to be achieved (at least in part) with this approach [31]. The conjugation of tuftsin with phosphorylcholine and the creation of TPC are reported by Segal et al. to attenuate inflammatory pathways by enhancing immune regulatory mechanisms. Thus, TPC presents a promising potential as a novel therapeutic agent for the effective treatment of various autoimmune diseases [32].

In conclusion

All published studies in this issue of Immunologic Research represent only a small piece of a big meeting. The International Meeting in Lisbon was indeed a special event, full of interesting discussions, collaborations, and expectations for the next meeting.

Compliance with ethical standards

Conflict of interest The author declare that they have no conflict of interest.

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