The First Israel-Greece Meeting: Collaboration at its Best

Elias Toubi MD

Division of Allergy and Clinical Immunology, Bnai Zion Medical Center, affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

KEY WORDS: autoimmunity, rheumatic diseases, biological therapies, regulatory mechanisms

IMAJ 2016; 18: 511–512

Collaborations between scientists from different countries are always a good reason to meet and to establish new bilateral projects and research plans. In this vein, Israeli and Greek rheumatologists and clinical immunologists met in the lovely city of Haifa on 14 and 15 October 2015 and established the first Israel-Greece meeting on advances in rheumatology and autoimmunity. Important issues were presented and discussed by both sides, illustrating that such discussions can move research forward, that science has no borders, and that medicine will always be a perfect vehicle for people from various countries to remain close friends. Some of the issues discussed are reported briefly below.

REGULATORY MECHANISMS IN AUTOIMMUNE DISEASES

Autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc) and others are considered to be a consequence of self-tolerance breakdown and the development of immune complexes and systemic inflammation. In these patients immune cells such as dendritic cells, T and B cells are over-activated, producing a wide range of pro-inflammatory cytokines [1]. In recent years, autoimmunologists switched their attention, focusing on the regulatory mechanisms, namely, the role of both T and B regulatory cells and their importance in preventing autoimmunity and inflammation [2,3]. Regulatory molecules/proteins such as semaphorin3A and CD72 are some of the recently investigated regulatory molecules, both expressed on and secreted by B regulatory cells. B regulatory cells were reported to be involved in the pathogenesis of RA and SLE through their failure to maintain self-tolerance and regulate autoimmunity [4,5].

At this meeting Lyn kinase was presented as one of the important regulatory factors in SLE. Lyn kinase is expressed on B cells, is part of the B cell receptor (BCR) activating complex, and is involved in the process of B cell proliferation. Lupus-like symptoms were described in a murine Lyn-/- model, showing that relevant autoantibodies were developed together with the deposition of immune complexes in the kidneys. In addition, B cells from human SLE patients were shown to have decreased Lyn expression as compared to normal B cells and to be associated with SLE disease activity [6]. The involvement of B cells, mainly B regulatory (Breg), in the pathogenesis of SSc was presented. B cells are involved in the development of fibrosis in SSc by producing autoantibodies that activate fibroblasts but also by cell-to-cell contact with fibroblasts. B cells can function as antigen-presenting cells to T cells and induce dendritic cell maturation that promotes Th2 response [7]. In contrast, IL-10 producing Breg cells were shown to be both numerically and functionally decreased in association with SSc disease activity, mainly SSc-associated interstitial lung disease. Furthermore, Breg numbers and function were negatively correlated with SSc-specific autoantibodies such as anti-topoisomerase I and anti-centromere antibodies [8].

THE IMPORTANCE OF SPECIFIC AUTOANTIBODIES IN AUTOIMMUNE DISEASES

The role of specific autoantibodies in defining autoimmune diseases, their development, prognosis and severity was also discussed. In this respect, certain autoantibodies are considered helpful in the classification of patients suffering from distinct clinical subtypes and may be useful in predicting response to treatment. Natural antibodies were reported at this meeting to play a significant role in the first-line defense against pathogens, in neutralizing tumor necrosis factor and in protecting against autoimmunity. Lower levels of natural autoantibodies are associated with the development of different autoimmune diseases. In contrast to natural autoantibodies, pathogenic autoantibodies recognize self-antigens with high affinity and thereby promote the development of inflammation. Reaching a definite diagnosis of autoimmune diseases is difficult in some cases and may require repeated evaluation of patients. In this case, some autoantibodies in conjunction with other clinical and laboratory findings were proved to be valuable in defining a definite diagnosis and in some cases the prognosis [9]. In relevance to this, primary Sjogren's syndrome negative for anti-Ro/SSA and anti-La/SSB antibodies is characterized by a lower risk of lymphoma and a lower level of B cell expansion [10].

Antiphospholipid syndrome (APS) was also discussed at this meeting, being characterized by the detection of specific autoantibodies such as lupus anticoagulant, anticardiolipin and anti-β2 glycoprotein antibodies (aPL). Women's issues were specifically discussed, e.g., the particular aspects of women with classical vascular APS, the long-term follow-up of women with obstetric APS, and the management of women with persistent antiphospholipid antibodies [11]. The histopathology of placentas of women suffering from APS was also reported. The diversity of the human placental aPL fingerprint suggests that multiple pathological processes may occur in pregnancies affected by aPL [12].

THE ROLE OF FACTORS AND PROTEINS IN AUTOIMMUNITY AND INFLAMMATION

High levels of circulating microvesicles (MVs), namely annexin V-bearing MVs, endothelial and platelet MVs, have been associated with an increased risk of thrombosis. An increased presence of endothelial MVs was also found in APS patients with recurrent thrombosis and pregnancy loss. Microvesicles play a role in both physiological and pathologic states. They are involved in regulating processes such as coagulation and angiogenesis, but also play a role in pathological states such as thrombosis and inflammation [13].

The discovery of useful biomarkers for assessing ongoing inflammatory and fibrosis activity in the skin and internal organs of SSc patients was one of the topics discussed at this meeting. In this respect, lysyl oxidaze (LOX), a copper-dependent amine oxidase, became a candidate biomarker for assessing fibrosis in SSc patients. LOX has been evaluated in several states of fibrosis, such as primary myelofibrosis, hepatic fibrosis and recently in lung fibrosis of SSc patients [14]. It was shown that elevated serum LOX levels correlated positively with SSc disease activity as well as with the extent of the lung and skin fibrosis that developed.

The role of prolactin and estradiol in Colombian women with SLE was discussed. Women of childbearing age are primarily affected, which raises the idea of a hormonal role in the development of SLE. Relevant hormones are prolactin, estradiol and progesterone. The authors found a significant association of decreased serum C4 levels, SLE disease activity, mainly in the kidney, and increased estradiol levels. However, no association was found between hyperprolactinemia and SLE disease activity. These findings suggest the possibility of implementing anti-estrogen therapy in such cases [15]. This question was discussed further, supporting the finding that increased estradiol levels are indeed associated with renal involvement in SLE. However, the association between prolactin levels and SLE disease activity is controversial and has yet to be established. Many studies support the finding of no association between increased prolactin in SLE and disease activity, while others show a higher prevalence of serositis, pericarditis, and proteinuria in SLE patients with hyperprolactinemia. The subject of hormone imbalance and SLE should be studied further [16].

INFECTIONS AND THE IMMUNE SYSTEM

Infections both viral and bacterial are closely associated with immune mediated and autoimmune diseases. In some cases they trigger autoimmune diseases and in others they present with many symptoms that may mask immune mediated diseases, such as long-lasting fever, arthralgia, and the presence of autoantibodies such as anticardiolipin antibodies, rheumatoid factor and others [17].

Case reports were presented describing the clinical courses of some infections, such as *Rickettsia sibirica mongolitimonae* which appeared to be an emerging pathogen in both southern and northern Greece. This pathogen should be considered in the differential diagnosis of any febrile illness [18]. In another case report, Kikuchi-Fujimoto disease, also known as histiocytic necrotizing lymphadenitis, is considered be a rare disease of unknown etiology. Such pathogens should be considered in the differential diagnosis of fever of unknown origin [19].

CONCLUDING COMMENTS

Both Israel and Greece are rich in ancient archeology, beautiful beaches, and good wine. This meeting added another common feature of our countries – both have an immense interest in rheumatology and the strong will to continue this collaboration. Here's looking forward to the second Israel-Greece meeting.

Correspondence
Dr. E. Toubi
Division of Allergy and Clinical Immunology, Bnai Zion Medical Center, Haifa 33394, Israel
email: elias.toubi@b-zion.org.il

References

1. Mackern-Oberti JP, Llanos C, Vega F, et al. Role of dendritic cells in the initiation, progression and modulation of systemic autoimmune diseases. *Autoimmun Rev* 2015; 14: 127-39.
2. Dhaeze T, Stinissen P, Liston A, Hellings N. Humoral autoimmunity: a failure of regulatory T cells? *Autoimmun Rev* 2015; 14: 735-41.
3. Vadasz Z, Toubi E. The many faces of B regulatory cells. *IMAJ* 2014; 16: 631-3.
4. Vadasz Z, Haj T, Balbir A, et al. A regulatory role for CD72 expression on B cells in systemic lupus erythematosus. *Semin Arthritis Rheum* 2014; 43: 767-71.
5. Catalano A. The neuroimmune semaphorin3A reduces inflammation and progression of experimental autoimmune arthritis. *J Immunol* 2010; 185: 6373-83.
6. Liossis S-NC, Konstantopoulou GM. The potential role of Lyn kinase in systemic lupus erythematosus. *IMAJ* 2016; 18: 513-15.
7. Sakkas LI, Bogdanos DP. Systemic sclerosis: new evidence reinforces the role of B cells. *Autoimmun Rev* 2016; 15: 155-61.
8. Sakkas LI, Bogdanos DP. The role of B cells in the pathogenesis of systemic sclerosis. *IMAJ* 2016; 18: 516-17.
9. Kapsogeorgou EK, Tzioufas A. Autoantibodies in autoimmune diseases: clinical and critical evaluation. *IMAJ* 2016; 18: 519-23.
10. Quartuccio L, Baldini C, Bartoloni E, et al. Anti-SSA/SSB-negative Sjogren's syndrome shows a lower prevalence of lymphoproliferative manifestations, and a lower risk of lymphoma evolution. *Autoimmun Rev* 2015; 14: 1019-22.
11. Papadakis E, Banti A, Kioumi A. Women's issues in antiphospholipid syndrome. *IMAJ* 2016; 18: 524-9.
12. Viall CA, Chaley LW. Histopathology in the placentae of women with antphospholipid antibodies: a systemic review of the literature. *Autoimmun Rev* 2015; 14: 446-71.
13. Aharon A, Brener B. Microvesicles in thrombosis and inflammation *IMAJ* 2016; 18: 530-3.
14. Rimar D, Rosner I, Slobodin G, et al. Lysyl oxidase in systemic sclerosis: getting under the skin. *IMAJ* 2016; 18: 534-6.
15. Aulestia C, De Zubiria A, Grandos C, Suarez J, Cervera R. Prolactin and estradiol profile in a Colombian women with systemic lupus erythematosus. *IMAJ* 2016; 18: 537-41.
16. Watad A, Amital H, Aljadeff G, Goddard G, Orbach H, Shoenfeld Y. Prolactin, another important player in the mosaic of autoimmunity [Editorial]. *IMAJ* 2016; 18: 542-3.
17. Bashi T, Bizzaro G, Ben-Ami Shor D, Blank M, Shoenfeld Y. The mechanisms behind helminth's immunomodulation in autoimmunity. *Autoimmun Rev* 2015; 14: 98-104.
18. Chochlakis D, Mantadakis E, Thomaidis S, Tselentis Y. Chatzimichael A, Psaroulaki A. First human case of *Rickettsia sibiris mongolotimonae* infection in northern Greece. *IMAJ* 2016; 18: 544-6.
19. Mahagna H, Neumann SG, Schiby G, Belsky V, Amital H. Kikuchi-Fujimoto disease, don't forget it in the differential. *IMAJ* 2016; 18: 547-8.

"Do unto those downstream as you would have those upstream do unto you"

Wendell Berry (born 1934), American novelist, poet, environmental activist, cultural critic, and farmer