

The Second Greek–Israeli Symposium on Autoimmunity and Rheumatology: Success Through Synergy

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On 14 September 2018 in the city of Larissa, Greece, just south of Mount Olympus, the second Greek–Israeli symposium on autoimmunity and rheumatology was held. Experts in the field of rheumatology and immunology discussed the novelties and advances in this field. The cross-cultural exchange of knowledge stimulated deeper appreciation of the current concepts in diagnosis and therapeutics for autoimmune diseases. Such exchange promotes collaboration and bridges connections between the scientific communities of the two countries [1] [Figure 1].

AUTOIMMUNITY: FROM MOLECULES TO CELLS, FROM DIAGNOSIS TO TREATMENT STRATEGIES

The novel immunomodulatory role of B-regulatory cells (B-regs) received extensive attention by Mavropoulos and colleagues [2] who presented data that highlighted the decrease of B-regs in psoriatic arthritis (PsA). The levels of B-regs inversely correlated with the psoriasis area of severity index, IL-17, and IFN- γ producing T-cells. Liossis et al. [3] expanded on the role of the B cell class on autoimmunity and stated that the majority of autoantibodies generally produced by immature B

Figure 1.
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cells are auto-reactive [4]. This phenomenon occurs as part of the natural random segment assortment to produce antibody specificities. Therefore, the presence of checkpoint regulation in B cell maturation maintains the efficient removal of those autoantibodies. Nevertheless, the absence of these mechanisms results in increased autoimmunity. The speaker explained the emergent role of the protein tyrosine phosphatase nonreceptor type 22 (PTPN22) and the risk allele, which encodes an R620W amino acid that results in high frequencies of autoreactive antibodies. This variant subsequently results in defective autoreactive B cell counterselection and thus promotes autoreactive B cell activation and production of autoantibodies [5].

Moving away from B cells, Sabag and colleagues [6] discussed the role of T-regulatory cells (T-regs) in psoriasis. In the presentation, the authors characterized abnormalities in the balance of T-regs in psoriatic skin [7]. Markers of T-regs, Semaphorin 3A, and neuropilin-1 were found to be significantly decreased in psoriatic skin when compared to normal skin. These findings were supported by the concomitant down-regulation of IL-10 expression. Vadasz and Toubi [8] expanded on the role of Semaphorin 3A by demonstrating its immunoregulatory role in inflammatory bowel diseases (IBD). Sera levels and the expression of T-regs was lower in IBD patients. Furthermore, its expression was found to be correlated with IBD disease activity. Combined, these findings provide an avenue of research for new promising therapeutic targets.

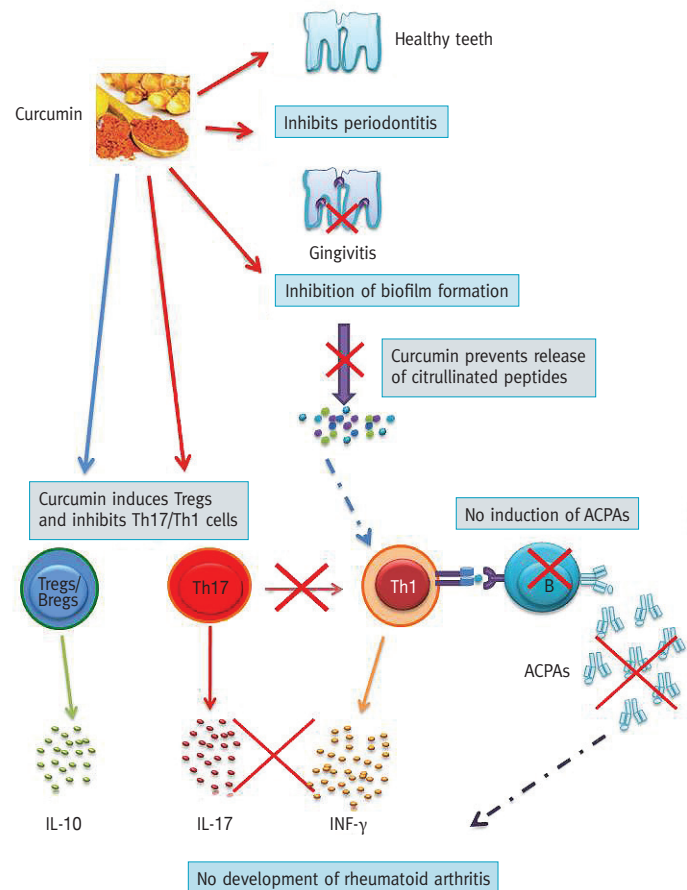
In the Greek capital of coffee, Sharif and colleagues [9] discussed the role of coffee consumption on autoimmune diseases. Caffeine, the psychoactive molecule in coffee, was shown to have an immunomodulatory role. In the presentation, Sharif touched on the protective role of coffee intake in multiple sclerosis (MS) disease development and progression, and in primary sclerosing cholangitis. Furthermore, coffee intake was shown to worsen disease outcome in rheumatoid arthritis (RA) as well as influence treatment with methotrexate. Moreover, coffee intake delayed the absorption of levothyroxine for Hashimoto's thyroiditis. These findings highlight the role of dietary molecules on the mosaic of autoimmunity.

AUTOIMMUNITY AND DIET: THE MICROBIOME

The role of diet and the microbiome on autoimmunity was discussed by Asteriou et al. [10] The team elaborated on the effect of various diets on the microbiome. They also expanded on the role of curcumin (turmeric) in the decrease of CD4+ T-cells. In addition, curcumin administration shifted the microbiome structure with increased abundance of certain bacterial families including *Prevotellaceae*, *Bacteroidaceae*, and *Rikenellaceae* [11] [Figure 2].

Prevotella strains have been shown to be constantly decreased in multiple sclerosis (MS) patients. Such species have been shown to be inversely correlated to Th17 expansion and disease activity. Therefore, a diet high in curcumin might be

Figure 2. The protective effect of curcumin against the development of rheumatoid arthritis, by influencing the microbiome and thus inhibiting the pro-inflammatory cascade



ACPAs = anti-citrullinated protein antibodies, B-regs = B-regulatory cells, T-regs = T-regulatory cells

considered as an adjunctive therapy in MS and in RA through its anti-inflammatory properties [12].

Also on the topic of microbiome, Blank et al. [13] expanded on the role of helminths on autoimmune diseases. Geopidemiological studies have shown low frequency of certain autoimmune diseases. One of the major hypotheses to explain this trend is the hygiene theory. Moreover, long-lived parasites, such as helminths, have the ability to immunomodulate host immunity, protecting themselves from elimination and minimizing severe pathology in the host.

In the last decades, many studies have reported that parasite infection in human, or systemic treatment with helminth extracts, can reduce inflammation associated with autoimmune diseases such as MS, RA, type 1 diabetes mellitus, and IBD. Helminths secrete several molecules, including phosphorylcholine. Blank's group [14] described a bifunctional molecule comprising phosphorylcholine conjugated to tuftsin. Tuftsin-

phosphorylcholine decreased disease activity in three murine experimental models of autoimmune diseases (e.g., lupus, collagen induced arthritis, and colitis) and ex-vivo human samples of giant cell arteritis. Its function is a result of phosphorylcholine activity through toll-like receptor 4 and tuftsin function via neuropilin receptor [14]. This new molecule holds great potential as a therapeutic treatment for autoimmune diseases.

The relationship between the microbiome and autoimmune diseases was further explored by Sakkas' group [15,16]. Human cytomegalovirus and Epstein-Barr virus are ideal candidates for involvement in systemic sclerosis (SSc) pathogenesis due to their lasting persistence through periods of latency and activation and due to their ability to manipulate innate and adaptive immunity [17]. Viral agents have been known to induce autoimmunity through various mechanisms including epitope sharing, stander effect, and molecular mimicry. In their experiments, the authors investigated the presence of autoantibodies against certain proteins of cytomegalovirus including UL-44, UL-57, and UL-83. No correlation of anti-UL57 seropositivity was demonstrated with demographic, clinical, or immunological features of SSc. Interestingly, immunoreactivity against UL-83 was found to be high and strong thus implying a possible pathogenic role in the disease [15,16].

AUTOIMMUNITY: DISEASE PATHOGENESIS

Highlighting the intercalating nature of autoimmune etiopathogenesis, Shoenfeld and colleagues [18-21] described the intricate interplay of the several components that resulted in autoimmune disease formation. The speakers described the integral role of genetic background, hormone status, and environmental factors as triggers of disease pathogenesis. Lifestyle and dietary factors seem to upset the immune system and result in immune dysregulation and subsequent disease occurrence in the genetically predisposed. Furthermore, Shoenfeld's group [22] introduced the concept of autoimmune/autoinflammatory syndrome induced by adjuvant (ASIA). Adjuvants, including infectious agents, silicone, and aluminum salts are associated with immune-mediated diseases. Four conditions including silicosis, Gulf War Syndrome, macrophagic myofascitis syndrome, and post-vaccination phenomenon have been shown to have related symptoms and share exposure to adjuvant material.

Several suggested criteria to diagnose ASIA have been proposed. Major criteria include exposure to adjuvants and appearance of typical manifestations including myalgia, arthralgia, fatigue, neurological manifestations, cognitive dysfunction, and pyrexia. Other elements in the major criteria include improvement of symptoms after removal of inciting agents and biopsy findings. Minor criteria include the appearance of autoantibodies of suspected adjuvant and specific human leukocyte antigen. Other clinical findings include IBD.

Watat et al. [23] corroborated the findings of Shoenfeld's group and presented a large database analysis on silicone breast

implants and the risk of development of autoimmune diseases. In their analysis, an increased risk of systemic sclerosis, Sjögren syndrome, and sarcoidosis was noted in subjects with silicone implants compared to age- and gender-matched individuals. These data, in combination with findings in animal models reported previously in the literature, highlight the relationship of silicone adjuvant to disease pathogenesis.

As one of the diseases induced by adjuvants, SSc is a rare autoimmune disease that is characterized by marked elements of vasculopathy, fibrosis of skin, and internal organs as well as production of autoantibodies. Plageras et al. assessed the genetic background of SSc through candidate gene studies and genome-wide association studies [24]. This combined method of genomic data analysis allows the identification of novel genetic foci, potential biomarkers of disease severity, and potential therapeutic agents. Daoussis and co-authors [25] expanded on the genetic pathways in SSc and presented data that suggested the role of Dickkopf-related protein 1 (DKK-1) downregulation at the edematous phase of the disease indicating the involvement of the Wnt pathway early in disease pathogenesis [26]. Moreover, DKK-1 expression is decreased in both affected and non-affected skin, suggesting that the whole skin is affected. Following B cell depletion therapy with rituximab, upregulation of DKK-1 expression is demonstrated, which is associated with enhanced resolution of skin fibrosis [27]. With regard to autoantibody profile in SSc, Gkoutzourelas et al. analyzed the epitope against which the autoantibody response is produced in patients with systemic sclerosis [28]. In their analysis, reactivity to Ro52-1 (amino acid 1-127) was present in 33.3% of anti-Ro60(+) patients and in 0% of anti-Ro60(-) patients. Anti-Ro52 is a characteristic antibody in patients with SSc [29].

AUTOIMMUNITY AND GENETICS

The role of genetic analysis was also discussed with regard to other autoimmune diseases, including MS. Dardiotis and colleagues [30] highlighted evidence implicating variant encoding for adhesion molecules responsible for lymphocyte adhesion and extravasation into the central nervous system in disease pathogenesis. Such adhesion molecules were shown to be related to disease severity, and their availability at the time of diagnosis could guide physicians toward a treatment regimen that identifies the aggressiveness of the disease and hence the appropriate treatment required.

Expanding on the treatment aspect of MS, Karussis et al. [31] outlined the emerging concept of immune reconstitution therapies, which is based on intermittently applied treatment regimens. The science behind the concept allows for the depletion of the immune system for the anti-inflammatory effect. During reconstitution, the immune system regains the ability to respond to infections and survey for cancer. Such treatment regimens have been shown to result in significant clinical efficacy. Moreover,

administration of therapy in pulses results in higher patient compliance and lower risk of cumulative dosing side effects.

Immunomodulatory drugs are known to have serious deleterious side effects on patients [32]. Tsouris et al. [33] investigated the incidence of autoimmune liver diseases in patients with MS. Among MS patients, eight were positive for anti-nucleic acid antibody and anti-PML antibody. He noted that the presence of those autoantibodies appears in low titers and their routine checking is not justified. However, he added that such findings should be considered before exposing patients to the new immunomodulatory drugs therapy.

AUTOIMMUNITY AND DISEASE MANAGEMENT

Speaking on newer aspects in disease management, Tektonidou and colleagues [34] described potential future treatment strategies in antiphospholipid syndrome (APS) including treatment with hydroxychloroquine, which was shown to inhibit platelet aggregation, activate toll like receptors, and prevent complement activation. In addition, statins inhibit endothelial and tissue factor activation, which play an integral role in the future treatment of APS. Case series and pilot studies have pointed to the role of B-cell depleting agents, complement inhibitors, mTOR pathway inhibitors, and neutrophil extracellular traps (NETs) inhibitors as potential therapeutic agents [35].

Boumpas et al. [36,37] expanded on the role of NETs in rheumatic diseases. Genome-wide association studies and gene expression analyses have implicated neutrophils and deregulated autophagy in autoimmune rheumatic diseases. Neutrophils have recently re-emerged as key players in the disease pathogenesis through putative effector functions including NETs [38]. NETs are networks of extracellular fibers comprised of extruded nuclear DNA and associated granular components, histones, and cytoplasmic proteins.

Neutrophils are rarely present in tissue biopsies from patients with lupus nephritis vasculitis or rheumatoid synovitis since these are short-lived cells. It has been shown that their remnants in the form of NETs are present in inflamed tissues. NETs represent a common denominator across different disorders; however, depending on the inflammatory context of each pathophysiologic condition, neutrophils may express and release through NETs distinct bioactive proteins involved in different biologic processes.

In RA, NET release has been shown to exacerbate T helper cell-mediated autoimmune responses by promoting dendritic cells maturation. Similarly, in systemic lupus erythematosus (SLE), NETosis has been shown to be correlated with increase expression of stress response protein REDD1. In systemic anti-neutrophilic cytoplasmic autoantibody (ANCA) vasculitis, it has been demonstrated that tissue factor expression in NETs and neutrophil derived microparticles promote thromboinflammation and the thrombophilic state associated with the disease. Vasilopoulos et al. described the

new developments in ANCA vasculitis including the central role NETosis in disease etiopathogenesis [39]. Moreover, he presented the most recent 2016 European League Against Rheumatism treatment recommendations. New therapeutic agents, including complement cascade inhibitors and newer biological therapies targeting eosinophils, have demonstrated efficacious results in patients with resistant disease as an add on therapy to immunosuppressives.

Also with regard to systemic vasculitis, Rimar et al. investigated the new potential role of nailfold video capillaroscopy in the diagnosis of systemic vasculitis [40]. In their study, systemic vasculitis was associated with the finding of rolling, microhemorrhage, capillary loss and angiogenesis. Moreover, they described a new pattern, pericapillary stippling, in the nailfold of patients with systemic vasculitis [Figure 3]. Such techniques provide an avenue for the detection of disease processes in patients who are not presenting with otherwise typical end-organ damage associated with systemic vasculitis, and thus provide more data regarding new target organs in well-known diseases.

AUTOIMMUNITY AND DIAGNOSTICS

Regarding new target organs in the field of rheumatology, Slobodin et al. [41] described the intrinsic role of entheses in disease pathogenesis of several rheumatic diseases including familial Mediterranean fever, gout, pseudogout, ankylosing spondylitis, and polymyalgia rheumatica [25,42]. Pertinent to diagnostics, Goules and Tzioufas [43] highlighted the increased tendency of Sjögren disease patients in the development of lymphoma. They also described several prognostic markers for the development of lymphoma in such patients. Patients with extra-epithelial systemic manifestations are more likely to develop lymphoma. Moreover, lymphadenopathy, Raynaud's phenomenon, anti-Ro or anti-La positivity, monoclonal gammopathy, and C4 hypocomplementemia have been significantly associated with increased risk of lymphoma development. The identification of prognostic markers allows for the prediction

Figure 3. Pericapillary stippling can be seen as pigmented dots round the capillary cap, presumably consistent with capillary leak due to vasculitis, that resulted in hemosiderin deposition



of lymphoma development and allows for early diagnosis and treatment when appropriate. Association between disease entities has also been demonstrated in other diseases. Kitas et al. described the impact of cardiovascular risk factors in RA [44]. Patients with RA are at increased risk of cardiovascular disease [45]. They need to be screened systematically and monitored individually for cardiovascular risk factors. Such factors require management to prevent the development of cardiovascular disease. Cardiovascular diseases generally tend to present in relatively older population. Porat-Katz et al. [46] described the burden of autoimmune rheumatic diseases in the elderly by highlighting the role of immunosenescence in inducing autoimmunity. The authors then expanded on autoimmune diseases related to age and explained management approaches and considerations, mainly highlighting the need for a completely different approach when treating the elderly [47].

CONCLUSIONS

The second Greek–Israeli symposium on autoimmunity and rheumatology that took place in Larissa, Greece, the city of Achilles and Hippocrates, encouraged the exchange of knowledge among experts in the field of rheumatology and clinical immunology. Such opportunities allow for the development of collaborations between the nations, thus promoting further advances in these fields. We look forward for the next meeting that will take place of Israel, the cradle of world religions and a center of scientific and technological achievements.

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Capsule

IFN-λs inhibit Hantaan virus infection through the JAK-STAT pathway and expression of Mx2 protein

Hantaan virus (HTNV), member of the newly defined *Hantaviridae* family within the order *Bunyvirales*, can cause a hemorrhagic fever with renal syndrome with high fatality rates in humans. However, no specific antiviral agents for HTNV infection are currently available approved by the U.S. Food and Drug Administration. Although interferon lambdas (IFN-λs) have been shown to induce an antiviral state against HTNV, the molecular mechanisms remain to be determined. In this study, Li et al. found that IFN-λs exerted its anti-HTNV effect by activating Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway-mediated antiviral immunity

in A549 cells. Simultaneously, IFN-λs downregulated suppressor of cytokine signaling proteins, which are the known negative feedback regulators of the JAK-STAT signaling pathway. In addition, the authors demonstrated the role of IFN-λs-induced myxovirus resistance 2 (Mx2, also known as MxB) protein as a potential inhibitor for HTNV infection. These findings indicate that IFN-λs play an important role in cellular defenses against HTNV infection at an early stage and that human Mx2 may represent a potential therapeutic target for HTNV infection.

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Capsule

Evaluation of the TLR negative regulatory network in CVID patients

Common variable immunodeficiency (CVID), a clinically symptomatic primary immunodeficiency disease (PID), is characterized by hypogammaglobulinemia leading to recurrent infections and various complications. Recently, some defects in the signaling of TLRs have been identified in CVID patients, which led Sanaei et al. to investigate the expression of TLR4 and 9 negative regulatory molecules and their upregulation status following their activation. Using TaqMan real-time PCR, *SOCS1*, *TNFAIP3*, *RFN216*, and *IRAK-M* transcripts among peripheral blood mononuclear cells (PBMCs) were measured with/without TLR4 and 9 activations. TLR4 and 9 were activated by lipopolysaccharide (LPS) and unmethylated CpG-oligodeoxynucleotide (CpG-ODN), respectively. Production of IFN-α and TNF-α cytokines, as a part of the functional response of mentioned TLRs, was also measured using ELISA. Deficient

transcripts of *IRAK-M* and *TNFAIP3* in unstimulated peripheral blood mononuclear cell (PBMC) and lower production of TNF-α and IFN-α after treatments were observed. Upregulation of *RFN216* and *TNFAIP3* after TLR9 activation was abnormal compared to healthy individuals. Significant correlations were found between abnormal *IRAK-M* and *TNFAIP3* transcripts, and lymphadenopathy and inflammatory scenarios in patients, respectively. It seems that the transcriptional status of some negative regulatory molecules is disturbed in CVID patients, and this result could be caused by the underlying pathogenesis of CVID and could involve complications like autoimmunity and inflammatory response.

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