EDITORIAL

Autoinflammation and Autoimmunity: Pathogenic, Clinical, Diagnostic and Therapeutic Aspects

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The third Israel-Italy Meeting on Advances in Autoimmunity and Rheumatology, organized by Professors Elias Toubi, Roberto Perricone and Yehuda Shoenfeld, has arrived. In the delightful setting of the Zabludowicz Center for Autoimmune Diseases at Sheba Medical Center, Tel Hashomer (Tel Aviv), physicians from Israel and Italy will share their expertise in several fields of Immunology and Rheumatology.

An area that has gained relevance in recent years is Autoinflammatory Diseases. Giat and Lidar [1] present a paper on cryopyrin-associated periodic syndrome, a rare, autosomal dominant, autoinflammatory disorder associated with mutations in the *NLRP3* gene. This condition results from an over-activation of the inflammosome, which leads to the secretion of interleukin (IL)-1β and IL-18, leading to chronic or recurrent systemic inflammation. The clinical manifestations may involve the skin, muscles, skeleton, joints, eyes and central nervous system (CNS), as well as progressive hearing loss. Although historically separated as three different syndromes – familial cold autoinflammatory syndrome (FCAS, also known as familial cold urticarial syndrome, FCU), Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disorder (NOMID, also known as chronic infantile neurological cutaneous and articular syndrome, CINCA) – today the common genetic basis, etiopathogenetic mechanisms, and treatment suggest that they may represent the spectrum of a unique syndrome. While anti-IL-1 agents, such as anakinra, rilonacept and canakinumab, are the mainstay of therapy in the cryopyrin-associated periodic syndrome, other treatments are currently under investigation.

In this context, Di Gangi et al. [2] evaluate the potential usefulness of adalimumab, an anti-tumor necrosis factor (TNF) agent, in another autoinflammatory disease: hyper-immunoglobulin D syndrome (HIDS). This is an autosomal recessive syndrome caused by specific mutations in the mevalonate kinase gene. Its main clinical feature is recurrent inflammatory attacks. Since unstimulated peripheral blood monocytes (PBMCs) from patients with inactive HIDS produce a complex network of inflammatory cytokines and undergo decreased apoptosis, the TNFα monoclonal antibodies, which indeed are able to induce apoptosis of lymphocytes, may be a valid therapeutic option. Further studies are warranted.

An interesting approach to treat autoinflammatory disorders is described by Bashi et al. [3]. Starting from the assumption that the aim of helminths is to survive in the host, thus inducing a tolerance scenario, and that their eradication is linked to the increase of autoimmune conditions in certain countries, helminth conjugates and ova may be a promising treatment for inflammatory bowel disease.

Cohen [4] proposes a shift in paradigm from a global suppression of the immune system, as we witness today, to a molecularly driven language of regulation. It was shown that the administration of a self-peptide to patients with new-onset Type 1 diabetes mellitus (T1D) could significantly arrest the autoimmune destruction of residual beta cells and enhance metabolic control of their diabetes. Cohen suggests that such peptides belong to the Immunological Homunculus; consequently, these self-antigens may function as immune modulators allowing such an apparently controversial result.

Galeazzi et al. [5] present another therapeutic strategy based on the selective delivery of an immunoregulatory cytokine to the sites of inflammatory disease. This newly developed treatment, Dekavil, an 'armed antibody', consists of the human F8 antibody (specific to the EDA domain of fibronectin, a marker of angiogenesis) fused to the anti-inflammatory cytokine interleukin-1. The interesting feature is its structure, which allows the delivery and accumulation of the lL-10 cytokine at the sites of disease. A phase Ib clinical trial with initial signs of therapeutic benefit is currently underway in patients with rheumatoid arthritis (RA).

In the search for a suitable treatment for psoriatic arthritis (PsA), a number of agents have been proposed so far. Sarzi-Puttini and colleagues [6] emphasize that despite the major role played by disease-modifying antirheumatic drugs (DMARDs) and anti-TNF, the clinical heterogeneity of PsA makes selecting the most appropriate treatment challenging. Studies on tocilizumab (anti-IL-6), rituximab (anti-CD20), abatacept (CTLA4/IgG), ustekinumab (anti-IL-12/23), IL-17 inhibitors and apremilast (phosphodiesterase 4 inhibitor) are ongoing with promising results.

The novel treatments for patients with autoimmune diseases not only seem to restore an immunological balance, but in some cases are so powerful as to repair the tissue damage. Aharoni and Arnon [7] report that glatiramer acetate can promote repair and remyelination in the inflamed CNS in multiple sclerosis (MS) and in its model experimental autoimmune encephalomyelitis (EAE). The authors suggest that glatiramer acetate affects myelination under inflammatory as well as non-inflammatory conditions, supporting the notion that repair process in the CNS can be up-regulated by therapy.

Among the drugs that have changed the therapeutic approach to autoimmune diseases is belimumab. This B cell modulator was recently approved for the treatment of SLE. Thanks to Andreoli et al. [8], the first Italian data on real life experience are now available. Their results in over 18 patients show a significant reduction in disease activity (measured by SLEDAI-2k) at 9 months follow-up with no specific concerns regarding safety. Nonetheless, the administration of the drug was discontinued in 3 patients (16.7%): in 2 cases because of high disease activity and in the third because of recurrent infections. Better-characterized data, with a longer follow-up, are urgently awaited.

Not only new drugs but also improved usage and knowledge of already used agents may change the course of disease and in turn, the management of our patients. Nalli et al. [9] have consolidated expertise in the field of obstetric antiphospholipid syndrome (APS). In this condition, low dose aspirin in association or not with low molecular weight heparin is still the gold standard even though up to 25% of APS women may suffer from recurrent pregnancy loss. Low dose corticosteroids, hydroxychloroquine, intravenous immunoglobulins (IVIg) and plasma exchange, either alone or in combination, should be considered in selected cases as they can improve pregnancy outcome. The concept of autoimmune pregnancy has seen the arrival on the scene of new actors, as addressed by De Carolis et al. [10]. Besides antiphospholipid antibodies, natural killer (NK) cells and anti-thyroid antibodies are associated with impaired outcome of pregnancy, and the treatment should aim at restoring the immune system balance during gestation.

Furthermore, if IVIg are a classical therapeutic option for a number of autoinflammatory/autoimmune conditions, the use of subcutaneous immunoglobulins (SCIg) has now gained attention. Gelardi et al. [11] present their experience with the use of SCIg in patients with refractory polymyositis/dermatomyositis. They suggest that patients with cancer-associated myositis, with recent cancer or with pre-neoplastic disease, patients in whom immunosuppressants or prolonged glucocorticoid treatment is contraindicated, and young women who wish to become pregnant, would benefit from first-line therapy with SCIg.

The capacity of immunoglobulins to restore a normal balance in the immune system is evident in the case of patients with common variable immunodeficiency (CVID). The standard treatment of these patients comprises the lifelong replacement with IVIg, which reduces the frequency of infections and the progression of complications, including lung disease. Dolcino et al. [12] evaluate the gene-expression profiles of 10 CVID patients, showing that a number of genes involved in the innate and acquired immune responses are differentially expressed after IVIg treatment. Moreover, a marked decrease in CD8+T cells, and an increase in CD4+T cells and centrocytes (CD23- CD27- IgM- IgD- B cells) were observed. Vadasz and Toubi [13] brilliantly depicted the key role played by B cells, focusing on B regulatory cells (Bregs). This subset of IL-10-producing B cells has been proved to prevent the induction of arthritis and to ameliorate established disease in syngeneic immunized mice with experimental arthritis. The authors showed a strict relationship between Bregs and semaphorin3A (a regulatory protein); however, the exact mechanisms by which Bregs play their role are still unclear.

Semaphorins, and especially semaphorin3A, are involved also in the pathogenesis of another condition mainly driven by an inflammatory process: systemic sclerosis (SSc). Vadasz and co-authors [14] evaluated the levels of semaphorin 3A in the serum and its expression on T regulatory cells, in SSc patients, healthy controls and SLE patients. They found that serum levels of semaphorin 3A were lower in SSc compared to healthy controls and similar to SLE, denoting an inefficient T regulatory activity in autoimmune diseases such as SSc.

Serpins (Serin protease inhibitors) represent another piece of the puzzle of autoimmunity. This is a wide group of structurally conserved molecules that have several functions in the homeostasis of living organisms, being also involved in regulation of cellular viability. Gatto [15] addresses SERPINB3 expression in SLE. Lymphocytes of affected patients have a reduced SERPINB3 expression that in turn may increase the autoantigen burden in lupus or B cell autoreactivity, suggesting that SERPINB3 can influence the SLE course, specifically lupus nephritis. This connection between Serpins and autoimmunity may link another autosomal dominant disorder with the spectrum of autoimmunity as well.

Hereditary angioedema (HAE) results from the congenital deficiency of the C1 Inhibitor (C1INH) component of the complement system. C1INH is itself a serine protease encoded by the *C1INH* gene, also called *SERPING1*, and low complement (due to complement activation) as well as an increased

association with "classic" autoimmune disorders have been described. Triggianese et al. [16] found enhanced production of autoantibodies in patients with HAE. Most probably, an increased activation of B cells in association with a high expression of TLR-9 is responsible of this phenomenon.

The increasingly close relationship between autoimmune and autoinflammatory disorders is no longer a surprise. Borella et al. [17] address the intricate pathways connecting the innate and the adaptive immunity. Evidence of common susceptibility genes, such as the nucleotide-binding oligomerization domain-like receptor protein 1 (NLRP1) associated with SLE; of shared environmental triggers, especially infectious agents; of the presence of similar symptoms; and of skin, musculoskeletal and gastrointestinal involvement suggest the use of similar therapies.

The recent identification of a new syndrome, namely Hyperferritinemic Syndrome, has opened a window in the understanding of autoimmune/autoinflammatory disorders. Rosario et al. [18] have indeed gathered under a single umbrella different conditions including sepsis, systemic inflammatory response syndrome (SIRS), multiorgan dysfunction syndrome (MODS), macrophage activation syndrome (MAS), adult-onset Still's disease (AOSD), and the catastrophic variant of the antiphospholipid syndrome (CAPS) characterized by markedly elevated levels of ferritinemia. The novel idea suggests a pathogenic role for ferritin in these conditions, a matter recently examined by Colafrancesco et al. [19]. They found that sCD163, a molecule exclusively expressed on cells of monocytic origin, is overexpressed in different inflammatory conditions including MAS, sepsis and AOSD. Since ferritin production seems to be related mainly to macrophage activation, the observation of a positive correlation between ferritin serum levels and sCD163 in AOSD may be the link to the macrophagic origin of ferritin.

It is evident that new actors are on the scene, including *Saccharomyces cerevisiae*, commonly known as yeast. This was recently included among the possible pathogenic agents in autoimmunity. Rinaldi [20] suggests that the molecular structure of some antigens of yeast overlap with some of the most common autoantigens such as the autoantigen U2 snRNP. These data are strengthened by the evidence of an increased prevalence of anti-*Saccharomyces cerevisiae* antibodies (ASCA) in a number of autoimmune disorders including SLE. The role of ASCA should be re-evaluated in clinical practice together with dietary recommendations in selected groups of patients.

The seminal role of autoantibodies in the pathogenesis of autoimmune diseases is clear when considering RA. Indeed, anti-citrullinated protein/peptide antibodies (ACPA/anti-CCP) are a hallmark of the disease and are believed to play a role in disease initiation and pathogenesis. Citrullination is the post-translational conversion of arginine to citrulline catalyzed by peptidylarginine deiminase (PAD), an enzyme up-regulated under inflammatory conditions. Gertel et al. [21] added a juicy aspect, closing the gap between cigarette smoking, citrullination, lung disease and RA. Indeed, cigarette smoking – an inducer of citrullination – is the dominant risk factor for chronic obstructive pulmonary disease (COPD). COPD has an increased prevalence in patients diagnosed with RA and RA is associated with an increased risk of COPD independently of smoking. The authors speculate that ACPA in COPD patients might contribute to the induction of an autoimmune response and that treatment against the citrulline-specific immune response could putatively be applicable for COPD patients.

Not only the smoking habit, but another plague of industrialized countries, obesity, can be associated with the recent outbreak of autoimmune diseases. Versini et al. [22] focus on this issue and on the capacity of white adipose tissue (WAT) to secrete numerous soluble mediators called adipokines, involved in many processes including immunity and inflammation. In their systematic literature review, they found that obesity might be responsible for a dysreguation of Th17/Treg balance, and that obesity has a higher prevalence in ACPA-negative RA patients, in multiple sclerosis, in psoriasis and psoriatic arthritis, and in SLE. Furthermore, obesity may promote inflammatory bowel diseases (IBD), T1D and Hashimoto thyroiditis. Obese patients exhibit a more severe course of RA, SLE, IBD, psoriasis and PsA and a reduced therapeutic response in RA, IBD, psoriasis and PsA. Thus, in the future management of autoimmune patients, dietary and lifestyle recommendations should be strongly considered.

Infections may be another *primum movens* leading to the production of autoantibodies. In several circumstances, different infectious agents have been associated with the onset of autoimmune diseases. Perricone et al [23] present the exceptional autoimmune condition in which the infectious agent is proven: rheumatic fever. In patients affected by this disease caused by the Streptococcus beta Haemolytic group A, several autoantibodies have been detected including anti-endothelial cell antibodies. These were demonstrated to be directed towards specific peptides of vimentin, cross-reacting with antigens of the pathogen. The infusion of these autoantibodies in Lewis rats appeared to provoke an experimental model of disease.

In another autoimmune condition, narcolepsy, the *Streptococcus spp.* as well as the H1N1 (both the infection and the vaccine) seem be the initial triggers. Arango et al. [24] underline the enormous role of genetic factors, namely, the allele HLA DQB1*06:02 in the disease pathogenesis.

Apart from the role as merely disease triggers, infections represent a major burden in patients with autoimmune diseases, such as SLE and RA. These patients have a higher morbidity and mortality linked to infections due to the imbalance in the immune system and the use of immunosuppressants. Barrett and collaborators [25] acquired data from the SEPSIS-ISR, an ongoing prospective study that collects data of all patients

admitted to intensive care units of seven major hospitals in Israel with the diagnosis of sepsis during the decade 2002–2012. Unfortunately, the data on the prevalence of sepsis were not available at the time of writing this editorial.

As a consequence of the role of infections in autoimmunity, their prevention, especially through vaccinations, has become a fundamental issue in the fight. However, an association has been shown between vaccines and autoimmunity that has led to the description of a new syndrome, ASIA, the Autoimmune/Inflammatory syndrome Induced by Adjuvants In this condition, autoimmune phenomena occur after exposure to an adjuvant, such as those contained in certain vaccines. Tomljenovic et al. [26] evaluate the association especially of hepatitis B virus vaccine and human papilloma virus vaccine with autoimmune diseases, in particular SLE. The adjuvants could be associated with specific tissue damage, acting as a Trojan horse, thus allowing the accumulation of toxic molecules in target organs. Despite the fact that the benefits from vaccination still largely overwhelm the risks, physicians should be aware of the possibility of an autoimmune reaction following vaccination.

Bar-On and co-workers [27] deal with the controversial topic of fibromyalgia (FM). This is a chronic debilitating disorder characterized by widespread pain, allodynia, hyperalgesia, fatigue, and unrefreshing sleep accompanied by mood and cognitive disturbances. The diagnosis is complex since there are specific tests, and the disease imposes a substantial financial burden. Another significant problem is the patients' limited adherence to treatment. Addressing compliance and adherence in such patients might lead to reduced health care costs and enriched quality of care.

In improving the management of autoimmune diseases, progress in diagnostic tools is much awaited. The limitation of inappropriate test requests and the imbalance between available economic resources and increasing health needs are jeopardizing modern health care services. Melegari and Bonaguri [28] performed a study aimed at unifying the testing algorithms, focusing on antinuclear antibodies (ANA), extractable nuclear antigens (ENA) and double-strand DNA (dsDNA). They conclude that strict cooperation between clinicians, laboratory specialists and health care services is crucial for the diffusion of ANA reflex testing.

We believe that a Meeting such as this helps build the wall of knowledge on Autoimmune and Rheumatic diseases. The sharing of ideas, the cooperation and the friendship are the cement that strengthens this wall every year.

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References

1. Giat E, Lidar M. Cryopyrin-associated periodic syndrome. *IMAJ* 2014; 16: 659-61.
2. Di Gangi M, Amato G, Converso G, et al. Long-term efficacy of adalimumab in hyper-immunoglobulin D and periodic fever syndrome. *IMAJ* 2014; 16: 605-7.
3. Bashi T, Blank M, Shoenfeld Y. Treating inflammatory bowel disease: from helminths to ova. *IMAJ* 2014; 16: 627-8.
4. Cohen IR. Arresting beta-cell destruction in Type 1 diabetes mellitus: mobilizing homuncular autoimmunity to treat autoimmune disease. *IMAJ* 2014; 16: 638-9.
5. Galeazzi M, Bazzichi L, Sebastiai GD, et al. A phase Ib clinical trial with Dekavil (F8-Il10), an immunoregulatory 'armed antibody' for the treatment of rheumatoid arthritis, used in combination with methotrexate. *IMAJ* 2014; 16: 666.
6. Sarzi-Puttini P, Atzeni F. New biological treatments for psoriatic arthritis. *IMAJ* 2014; 16: 643-5.
7. Aharoni R, Arnon R. Enhanced myelination in autoimmunity and in normal development induced by glatiramer acetate. *IMAJ* 2014; 16: 611-13.
8. Andreoli L, Reggia R, Pea L, et al. Belimumab for the treatment of refractory systemic lupus erythematosus: real-life experience in the first year of use in 18 Italian patients. *IMAJ* 2014; 16: 651-3.
9. Nalli C, Tincani A. Pregnancy in antiphospholipid syndrome: can we progress in patient management? *IMAJ* 2014; 16: 614-5.
10. de Carolis C, Perricone C, Perricone R. War and peace at the feto-placental front line: recurrent spontaneous abortion. *IMAJ* 2014; 16: 667-8.
11. Gelardi C, Paolini L, Danieli MG. Subcutaneous immunoglobulin G in idiopathic inflammatory myopathies: therapeutic implications. *IMAJ* 2014; 16: 646-7.
12. Dolcino M, Puccetti A, Ottria A, Barbieri A, Patuzzo G, Lunardi C. Modulation of adaptive immune response following intravenous immunoglobulin therapy in common variable immunodeficiency. *IMAJ* 2014; 16: 648-50.
13. Vadasz Z, Toubi E. The many faces of B regulatory cells. *IMAJ* 2014; 16: 631-3.
14. Vadasz Z, Rimar D. New potential biomarkers for disease activity and fibrosis in systemic sclerosis. *IMAJ* 2014; 16: 629-30.
15. Gatto M. Serpins as players in autoimmune diseases. *IMAJ* 2014; 16: 656.
16. Triggianese P, Guarino MD, Ballanti E, Chimenti MS Perricone R. Hereditary angioedema and autoimmunity. *IMAJ* 2014; 16: 622-4.
17. Borella E, Palma L, Zen M, et al. The body against self: autoinflammation and autoimmunity. *IMAJ* 2014; 16: 608-10.
18. Rosário C, Shoenfeld Y. The hyperferritinemic syndrome. *IMAJ* 2014; 16: 664-5.
19. Colafrancesco S, Priori R, Alessandri C, et al. The hyperferritinemic syndromes and CD163: a marker of macrophage activation. *IMAJ* 2014; 16: 662-3.
20. Rinaldi M. Anti-*Saccharomyces cerevisiae* autoantibodies and autoimmune diseases: the sweet and sour of baking yeast. *IMAJ* 2014; 16: 616-18.
21. Gertel S, Amital H. Putative approaches to bypass the citrulline-specific autoimmune response in rheumatoid arthritis [Review]. *IMAJ* 2014; 16 (9): 587-90.
22. Versini M, Aljadeff G, Jeandel PY, Shoenfeld Y. Obesity: an additional piece in the mosaic of autoimmunity. *IMAJ* 2014; 16: 619-21.
23. Perricone C, Rinkevich-Shop S, Blank M, et al. The autoimmune side of rheumatic fever. *IMAJ* 2014; 16: 654-5.
24. Arango MT, Kivity S, Chapman J, Shoenfeld Y. Narcolepsy: genes, infections and vaccines – clues for a new autoimmune disease. *IMAJ* 2014; 16: 636-7.
25. Barrett O, Abramovich E, Dreiher J, Novack V, Abu-Shakra M. Mortality due to sepsis in patients with systemic lupus erythematosus and rheumatoid arthritis. *IMAJ* 2014; 16: 634-5.
26. Tomljenovic L, Arango MT, Agmon-Levin N. Vaccination in autoimmune animal models. *IMAJ* 2014; 16: 657-8.
27. Bar-On Y, Shalev V, Weitzman D, Chodick G, Amital H. Old obstacles but new hopes: trying to understand the fibromyalgia construct. *IMAJ* 2014; 16: 625-6.
28. Melegari A, Bonaguri C. Harmonization of autoimmune diagnostics with antinuclear antibody testing algorithm: approach of appropriateness and clinical relevance. *IMAJ* 2014; 16: 640-2.

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