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Elias Toubi MD[1] and Yehudit Monselise MD[2]

[1]Division of Allergy and Clinical Immunology, Bnai Zion Medical Center, Haifa, Israel
Affiliated to Technion Faculty of Medicine Haifa, Israel
[2]Clinical Immunology Laboratory, Rabin Medical Center (Beilinson Campus), Petah Tiqva, Israel

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The European Workshops for Rheumatology Research are a wonderful tradition. Each year, a different European city hosts world-renowned rheumatologists and researchers in order to discuss new developments in rheumatology. This year's hosts – Gerd R. Brumester, Thomas Dorner and Andreas Radbruch – organized an excellent meeting in the beautiful city of Berlin, Germany at the Brandenburg Academy of Sciences. One hundred and ninety rheumatologists and researchers actively participated in the discussions, paying special attention to the following subjects in various sessions: B cells, T cells, Dendritic cells and antigen presentation, Apoptosis and innate immunity, Functional genomics, and Novel therapies.

The B Cells session

Andreas Radbruch (Berlin) opened the session by discussing the role of plasma blasts and plasma cells in humoral immunity. Peripheral plasma blasts (CD19+CD27+) were defined as a marker of systemic lupus erythematosus activity. They increase twofold in SLE patients compared to healthy individuals and in active SLE patients compared to inactive patients. Less than 60% of splenic antibody-secreting cells were short-lived plasma blasts, whereas 40% were non-dividing, long-lived plasma cells with a half-life of more than 6 months. Together with his team, Dr. Radbruch identified NZB/W mice with a fraction of long-lived DNA-specific plasma cells that were resistant to immunosuppressive therapy such as cyclophosphamide. However, short-lived plasma blasts were sensitive and easily eliminated by the same therapy. Plasma cells that migrate into the bone marrow or into chronically inflamed tissues usually survive for longer periods. The potential of these long-lived plasma blasts to migrate into the bone marrow and into chronically inflamed tissues was found to be regulated by chemokine receptors. In addition, it was shown that plasma cell survival in bone marrow and inflamed tissues is dependent on cytokines such as interleukins 2 and 10 and interferon-gamma. Long-lived autoreactive plasma cells should therefore become the relevant therapeutic target for the efficient treatment of SLE.

Gregg Silverman (La Jolla, CA, USA) discussed the mechanisms for inducing B cell death in the context of a therapeutic approach for autoimmune diseases. Recent reports on the success of B cell depletion by anti-CD20 (rituximab) in the treatment of rheumatoid arthritis encouraged successful implementation of this strategy in the treatment of other autoimmune diseases such as SLE. He discussed a different approach for B cell depletion by inducing B cell death using a B cell super-antigen. In order to understand how a B cell super-antigen affects the host immune system, mice were infused with protein A of *Staphylococcus aureus*, and the fate of peripheral B cells expressing B cell receptors with VH regions capable of binding *S. aureus* followed. Within hours, a rapid down-regulation of B cell receptors and co-receptors was demonstrated in *S. aureus*-binding splenic B cells, limiting their activation and proliferation. Enhanced B cell apoptosis was to develop through increased mitochondrial membrane permeability, caspase activation, and DNA fragmentation. B cell apoptotic bodies were deposited in the spleen, lymph nodes, and Peyer's patches. These studies defined a pathway for B cell receptor-mediated programmed cell death, that is, the VH region targeted by a super-antigen. It was shown that single high doses of *S. aureus* induce net supra-clonal B cell deletion, whereas single low doses of *S. aureus* induce supra-clonal proliferation that is later followed by deletion. Further studies are needed to determine whether microbial toxins that target V region-associated B cell receptor sites could be used as a new therapeutic approach by interfering with host immune responses in autoimmune diseases.

Simon Fillatreau (Berlin) presented his group's experience on the role of IL-10 production by B cells in the control of central nervous system autoimmunity. Experimental allergic encephalomyelitis is an inflammatory disease of the central nervous system and is often used as an animal model for multiple sclerosis, where autoreactive lymphocytes recognize myelin self-antigens. Th2 type cytokines, namely IL-4 and IL-10, have been suggested to play a role in regulating EAE. It was found that IL-10 but not IL-4-deficient mice had accelerated EAE following immunization with myelin

SLE = systemic lupus erythematosus

IL = interleukin
EAE = experimental allergic encephalomyelitis

oligodendrocyte glycoprotein. The acceleration of EAE in IL-10-deficient mice was associated with a decrease in IL-4 and an increase in IFNγ production in response to MOG antigen. These results suggest that IL-10 plays a crucial role in the progression and recovery of EAE and could therefore be used to interfere with inflammation.

Session on Dendritic Cells and Antigen Presentation

Juergen Schmitz (Bergisch-Gladbach, Germany) reviewed the diversity of human dentritic cells. DCs from both myeloid and lymphoid hematopoietic lineages are professional antigen-presenting cells, linking innate and adaptive immunity. They determine the balance between the tolerance and autoimmunity, depending on their stage of maturation and production of cytokines. Using specific markers and following their maturation in peripheral blood, DCs are classified into *immature DCs*, *semi-mature* DCs, and *mature* DCs. Immature DCs have the ability to present, endocytose and phagocytose antigens. They are of high intracellular major histocompatibility complex class II, express low CD40, CD80 and CD83, high chemokine receptors such as CCR1, CCR5 and CCR6, and secrete many cytokines. Whereas both iDCs and semi-mature DCs are T cell tolerogenic, mature DCs induce T cell activation and, under special conditions when over-activated and in susceptible individuals, result in a tolerance breakdown and the development of autoimmunity. In contrast to iDCs, mature DCs express high surface MHC II and CD40, CD80 and CD83. On the other hand, they lack efficient phagocytosis and endocytosis abilities. In addition, peripheral blood DCs are categorized into two major subsets. The first is BDCA1+ CD11c+ CD123 low (myeloid, mDCs), known to be IL-12, IL-10 and IL-6 inducers. The second is BDCA4+ CD11c- CD123 high (plasmacytoid, pDCs), which produces large amounts of type I IFNs (IFNα/β), and tumor necrosis factor.

In a study by Lebre et al. (Amsterdam, The Netherlands) it was shown that both subsets are preferentially localized in the synovium of rheumatoid arthritis patients, suggesting that they play a role in stimulating memory T cells and sustaining inflammation. In another study Jongbloed and collaborators (Glasgow, UK) demonstrated a decrease in both mDCs and pDCs in the peripheral blood of RA patients, whereas mDCs were increased in the synovial fluid, pointing to their role in maintaining chronic arthritis. Therefore, it is possible to assume that the targeting of synovial DCs following a better understanding of their biology may be a novel strategy in the treatment of rheumatic diseases.

IFN = interferon-gamma
MOG = myelin oligodendrocyte glycoprotein
DCs = dentritic cells
iDCs = immature dentritic cells
MHC = major histocompatibility complex
mDCs = myeloid dentritic cells
pDCs = plasmacytoid dentritic cells
RA = rheumatoid arthritis

The T Cells session

This session reviewed the role of different T cell subsets and their cytokine profile in the pathogenesis of RA. Pierre Miossec (Lyon, France) discussed the role of IL-17-producing T cells in the progression of chronic inflammatory arthritis. By producing IL-17, this unique subset of memory T cells induces different functions such as the activation of macrophages, increased IL-12 production, and the proliferation of fibroblasts. It is speculated that IL-17 + IFNγ + CD4+ T cells are produced in the inflamed synovium and play a role in the evolvement of synovial inflammation in RA. The role of this subpopulation has to be further defined and investigated.

Dr. von Boehmer (Boston, MA, USA) reviewed the role of regulatory T cells in manipulating autoimmunity. CD4+CD25+ T regulatory cells were shown to inhibit autoreactive CD4+ T cell proliferation and pro-inflammatory cytokine production, but did not enhance their apoptosis. In this regard, Cao et al. (Karolinska Hospital, Stockholm, Sweden) demonstrated an enrichment of CD25bright CD4+ T cells with the capacity to control T cell proliferation in the joints of patients with RA. Further extension of this observation was the finding of higher frequency of CD25bright CD4+ T cells in synovial fluid as compared with peripheral blood. The accumulation of these cells in joints indicates their capacity to suppress cytokine secretion and local inflammatory processes.

Session on Apoptosis and Innate Immunity

This session was opened by Diego Kyburz (Zurich, Switzerland) who reviewed the role of innate immunity in RA, namely the activation of synovial fibroblasts via Toll-like receptors. Increased IL-6 production from synovial fibroblasts was observed when TLR-2 (over-expressed on synovial fibroblasts of RA patients) was stimulated by bacterial peptidoglycan, and anti-TLR-2 inhibited this secretion.

Radstake et al. (Nijmegen, The Netherlands) investigated the role of TLR-4 in RA, namely, the relationship between the TLR4 Asp299Gly (896A>G) polymorphism and RA susceptibility. They performed genotyping (TLR-4 genotyping of the A>G polymorphism at position 896 of the TLR-4 gene) on RA patients from an early RA inception cohort and compared it to that of healthy blood donors. They found that the frequency of TLR-4 Asp 299 Gly polymorphism was significantly lower among RA patients than among controls, concluding that TLR-4 polymorphism influences the susceptibility to, but not the severity and outcome of RA.

Thomas Pap (Magdeburg, Germany) discussed the regulation of apoptotic cell death in RA synovial fibroblasts. He identified a downstream anti-apoptotic molecule SUMO-1 (small ubiquitin-like modifier), which, by interfering with Fas-receptor expression on synovial fibroblasts, can alter their sensitivity to undergo apoptosis. The over-expression of SUMO-1 on synovial fibroblasts inhibited their Fas-receptor expression and therefore their sensitivity to undergo apoptosis. A reversal of SUMO-1 expression restored the sensitivity of fibroblasts for apoptosis.

TLR = Toll-like receptors
SUMO = small ubiquitin-like modifier

Session on Novel Therapies

Sir Ravinder Maini (London, UK) opened the session with a review and summary of recent anti-inflammatory treatments employed by rheumatologists. The combination of two immunosuppressive therapies and the wide usage of anti-TNF treatments made great strides towards improving the prognosis of severe RA and resulted in better remissions. He also discussed the recent developments in the use of autologous stem cell transplantation in patients who are severely resistant to other therapies. The possible usage of T regulatory cells, the targeting of co-stimulatory molecules, and gene therapy were also mentioned.

P. Sidiropoulos et al. (Heraklion, Greece) presented their results on the safety and initial efficacy of a triple therapeutic regimen with anti-TNF, methotrexate, and cyclosporine-A. Sixteen patients completed 12 weeks of triple therapy. Three patients discontinued treatment because of adverse events. Seven of the 16 patients (44%) achieved a moderate response according to the EULAR response criteria. This encourages the addition of cyclosporine-A to maximum combination therapy of anti-TNF and methotreaxate in active RA. The role of CD25+ regulatory T cells in immunomodulating autoimmune diseases was discussed by Morgan et al. (Leiden, Netherlands) who analyzed the ability of CD4+CD25+ T cells to modulate collagen-induced arthritis. Depletion of CD25 + cells before collagen-induced arthritis induction led to the worsening of arthritis compared to the non-depleted control mice. The disease was significantly milder when CD4+CD25+ T cells were therapeutically transferred to mice. Thus, T regulatory cells modulate chronic arthritis and should be considered in a wide spectrum of autoimmune diseases. The use of Abatacept (a selective co-stimulation modulator, CTLA 4Ig) treatment for increasing the remission rate in RA patients, who were previously refractory to methotrexate treatment, was presented by Westhovens et al. (a phase II European multicenter study). Abatacept-treated patients showed a progressive increase in remission rates of up to one year.

Long-term immune reconstitution in patients treated with autologous stem cell transplantation for refractory autoimmune diseases was presented by Alexander and colleagues (Charite, Berlin). They performed a detailed evaluation of the newly developing immune systems in patients following immune ablation and subsequent autologous stem cell transplantation for severe autoimmune diseases. Autoreactive memory and effector lymphocytes were efficiently eliminated and the newly generated immune system in responding patients was tolerated for auto-antigens and was able to react to pathogens. Autologous stem cell transplantation can induce stable long-term clinical and serologic remission in patients with severe, standard therapy-refractory autoimmune diseases.

Peter Lipsky (Bethesda, MD, USA) concluded the meeting by providing a fascinating tour into the history of RA research, emphasizing the enormous development in both the understanding of RA pathogenesis and the use of new treatments. He assumed that with this development, including the initiation of many recent and new therapies, we should expect RA to be fully cured sometime in the near future.

TNF = tumor necrosis factor

Correspondence: Dr. E. Toubi, Division of Clinical Immunology, Bnai Zion Medical Center, P.O. Box 4940, Haifa 31048, Israel.
Phone: (972-4) 835-9253
Fax: (972-4) 835-9659
email: elias.toubi@b-zion.org.il