of ACPA. This initial development of auto-immunity appears to be independent of the disease-predisposing HLA-molecules. In most patients, this early event generates a polyclonal yet limited, mostly low-level autoantibody response that can be present for many years in the absence of clinical symptoms. Upon a putative second trigger, the ACPA epitope recognition repertoire broadens, more isotypes are being used, and ACPA serum levels rise. This is followed by precipitation of disease and is likely associated with the presence of the predisposing HLA-molecules. While the nature of this second trigger is presently unknown, the second event that initiates the broadening of the auto-immune response, in particular the citrulline-specific immune response, could mark a crucial moment upon which the auto-immune response becomes self-perpetuating and, potentially, irreversible.

Despite the many facets of ACPA revealed in the past two decades summarized above, it is not known how a breach of tolerance towards citrullinated proteins is mediated, or how ACPA-producing B-cells emerge.

Provision of T-cell help is crucial to convey the ability to B cells to modify the B cell receptor through somatic hypermutation. At present, it is unknown how ACPA- or other Anti-Modified Protein Antibody (AMPA)-producing B cells are "helped" by CD4+ Thelper cells, but it is often speculated that an auto-reactive T-cell response is crucial for their appearance. Our recent data show that such help could be provided by T-cells recognizing foreign proteins that have undergone a post-translational modification. In mice, AMPA-responses recognizing modified self-proteins are readily induced by immunization with modified proteins of non-selforigin. This is explained by the observation that the murine AMPA-response was, both at the monoclonal- and polyclonal level, highly cross-reactive towards multiple modified proteins, including proteins of self- and foreign origin. A similar observation was made analyzing the AMPA response in sera from RA patients. These data are important as the cross-reactive nature of AMPA could explain how autoreactive B-cell responses against PTM self-proteins can be induced by exposure to PTM foreign proteins thereby providing new insights on the breach of autoreactive B-cell tolerance.

Taken together, the analysis of the fine-specificity and recognition pattern of antibodies against modified proteins in RA during different phases of disease, together with detailed studies on the the identification, isolation and phenotypic characterization of auto-reactive B cells that express AMPA starts to shed light on the earliest phases of autoimmunity in RA.

Disclosure of Interest: None declared

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SP0146 CAN WE PREDICT WHO IS GOING TO DEVELOP RHEUMATOID ARTHRITIS?

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To accurately predict disease development can be considered the "holy grail" of risk factor research. It holds the potential to employ preventive treatment thereby nipping RA in the bud.

This presentation will review familial risk in RA and the underlying genetic risk factors, as well as environmental risk factors for disease. Autoantibodies are a potent prognostic marker when it comes to the risk of developing RA, and play a key role in current pathophysiological hypotheses. The newest players in the autoantibody field, and latest concepts of how the various risk factors contribute to disease onset will be discussed.

Disclosure of Interest: None declared

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SP0147 CAN WE PREVENT THE ONSET OF RHEUMATOID ARTHRITIS IN HIGH RISK INDIVIDUALS?

K.D. Deane. *Division of Rheumatology, University of Colorado Denver, Aurora, United States*

Multiple studies have demonstrated that rheumatoid arthritis (RA) related biomarkers can identify individuals without inflammatory arthritis who are at high-risk for the future development of clinically apparent synovitis and classified RA. These findings have led to the development of several prevention trials in RA that have either been completed, or are underway. With these exciting developments as background, this lecture will discuss multiple aspects of RA prevention including the role of biomarkers and other factors in developing robust prediction models for future RA, and methods to identify individuals before they develop RA. In addition, this lecture will discuss specific preventive approaches to RA such as clinical trial design and choice of preventive interventions that are based on our growing understanding of the mechanisms of RA development.

Disclosure of Interest: None declared

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SP0148 PATHOPHYSIOLOGY OF ESTABLISHED RA SYNOVITIS

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Access to synovial tissue through - minimally invasive - synovial biopsy procedures led to the implementation of new translational approaches to our understanding of established RA. In this lecture, we will illustrate how the identification of different synovial pathotypes and related molecular pathways translated into clinically relevant phenotypes, such as disease severity or response to therapy. Validation of these concepts in ongoing large-scale multi-centric trials will be key to the integration of synovial assessment tools in clinical practice.

Disclosure of Interest: B. Lauwerys Shareholder of: DNALytics

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FRIDAY, 16 JUNE 2017

Laboratory course - from the clinic to the lab and back II

SP0149 NEW TRENDS IN BIOMARKERS IN INFLAMMATORY JOINT DISEASES

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This lecture provides an overview on new developments in biomarker research and standardization in inflammatory joint diseases. The presentation includes an introduction of established and new biomarkers in serum and synovial fluid as well as methods for their detection. Furthermore, an overview on different modifications of auto-antigens (including citrullinated and carbamylated isoforms) and their role in immune response and pathogenesis of disease will be given. The diagnostic performance of new and established biomarkers will be discussed including antibodies against modified antigens also illustrated by difficult to diagnose cases. In this context, special attention will be attributed to the predictive value of biomarkers for diagnosis of disease and treatment response.

Disclosure of Interest: None declared

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FRIDAY, 16 JUNE 2017

Switching T on and off: how T cells drive and regulate chronic inflammation

SP0150 TH17 CELLS DRIVE AND REGULATE TISSUE INFLAMMATION

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Recently a subset of interleukin (IL)-17-producing T cells (T_H17) distinct from T_H1 or T_H2 cells was described and shown to have a crucial role in the induction of autoimmune tissue injury. Accumulating data suggests that there are three distinct steps in Th17 differentiation: *Induction*, *Amplification* and *Stabilization* mediated by distinct cytokines. Whereas TGF-b + IL-6 or IL-1 + IL-6 induces them, IL-21 amplifies Th17 cells, IL-23 stabilizes the phenotype of Th17 cells. Loss of any of the cytokines (TGF-β, IL-1, IL-6, IL-21 or IL-23) in the pathway results in a defect in generation of Th17. However not all Th17 cells are pathogenic and induce autoimmunity, IL-23 is a key cytokine that induces pathogenicity in Th17 cells (Lee et al., 2012). Using expression profiling at very high temporal resolution, novel computational algorithms and innovative nano-wire based "knock-down" approaches, we have developed a regulatory network that governs the development of Th17 cells. In addition to high-density temporal microarray analysis, we have performed single-cell RNA-seq of Th17 cells in order to characterize cellular heterogeneity, identify subpopulations, functional states and learn how gene expression variation affects Th17 effector functions. We have identified novel regulators of Th17 cells both *in vivo* and *in vitro* that do not affect Th17 differentiation but affect pathogenic vs. non-pathogenic functional states of Th17 cells. Some of the regulators that make Th17 cells non-pathogenic are also utilized by CD8+ T cells to induce T cell "exhaustion" or "dysfunction". These novel inhibitory molecules cooperate with other known "check-point" co-inhibitory receptors to suppress anti-tumor immunity.

Disclosure of Interest: None declared

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SP0151 SWITCHING OFF UNWANTED IMMUNE RESPONSES: THE MECHANISM OF ANTIGEN-SPECIFIC IMMUNOTHERAPY WITH T CELL EPITOPES

D.C. Wraith. *Institute of Immunology & Immunotherapy, University of Birmingham, Birmingham, United Kingdom*

Control of autoimmune and allergic conditions can be reinforced by tolerance induction with peptide epitopes; this presentation will focus on the mechanisms involved. Peptides must mimic naturally processed epitopes. Peptide induced peripheral tolerance is characterised by the generation of anergic, IL-10 secreting $CD4^+$ T-cells with regulatory function. $CD4^+$ T-cells become anergic following their first encounter with peptide. The loss of proliferative capacity correlates with a cytokine switch from a pro-inflammatory to a phenotype characterised by secretion

of the anti-inflammatory cytokine IL-10. IL-10 Treg/Tr1 cells suppress dendritic cell maturation, prevent Th cell differentiation and create a negative feedback loop for Th driven immune pathology. Tolerance induction involves upregulation of transcription factors controlling IL-10 and inhibitory receptors limiting T cell signalling. Results from clinical trials of peptide immunotherapy will be discussed.
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SATURDAY, 17 JUNE 2017

Reverse translation - learning from clinical trials in SLE, Sjögren's and APS

SP0152 LEARNING FROM CLINICAL TRIALS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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An enormous sense of frustration has surrounded the results of clinical trials in patients with systemic lupus erythematosus (SLE). A steady stream of trials including those studying the effects of Epratuzumab, Abatacept, Rituximab, Tabalumab and Silfalimumab have failed to meet their endpoints. Even though Benlysta (which blocks the B-cell activating factor BAFF) did meet its endpoints, it only demonstrated a difference of around 10% between the Benlysta-treated and placebo-treated arms in trials involving over 800 patients.
However, there are some bright spots on the horizon. Trials comparing the use of Mycophenolate with other classic immunosuppressive drugs clearly showed it to be as good as Cyclophosphamide in getting patients into renal remission and demonstrated its superiority in maintaining that remission compared to Azathioprine[(1)]. The use of Atacicept which blocks two B-cell activating factors has shown some extremely promising results[(2)] as have trials of both Rontalizumab and Anifrolumab[(3)] (which block interferon-alpha).
Some key messages learnt from the running of the lupus trials include the importance of minimising the concomitant steroids and immunosuppression; ensuring the quality of those assessors participating in the clinical trials and the utility of employing an independent peer-review panel to monitor data as it is collected from the participating centres during the course of the trial. It is also evident that selecting patients who are more serologically active is likely to be of benefit both in clinical trials and in the clinic. However, we still need better biomarkers to help guide us; the identification of individuals expressing a high interferon alpha signature (and who thus might better benefit from an interferon alpha blocker) is one such example.
It remains ironic that Rituximab, the most widely used monoclonal antibody in SLE, failed its endpoint in two clinical trials. However, detailed analyses of data from those trials have shown some encouraging trends including falls in dsDNA antibodies and improvement in some clinical parameters.
References:
[1] Dooley MA et al. N Engl J Med 2011; 365; 188.
[2] Isenberg et al. Ann Rheum Dis 2015; 74; 2006–18.
[3] Furie R et al. Arthritis Rheum 2015; 67 (suppl 10) (abstract).
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SP0153 LESSONS FROM APS TRIALS

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Prevention of thrombosis in patients with APS remains a vexing clinical problem. In patients with a history of thrombosis, there is considerable risk of recurrence, and long-term anticoagulation treatment with warfarin is effective in most cases. Existing evidence suggest that the use of DOACs for secondary thromboprophylaxis for APS patients with previous VTE is promising. Until new data from ongoing clinical trials are available, there is not enough evidence to consider using DOACs in patients with APS and previous arterial events. The efficacy of heparin and low-dose aspirin in APS patients with previous pregnancy losses is supported by 3 meta-analysis available on the topic. In patients with antiphospholipid antibodies but without a previous thrombotic event, most physicians in the field recommend thromboprophylaxis with low-dose aspirin. Given the diversity of clinical presentations and medical specialties involved, it is not surprising that treatment of APS has been subject of intense debate. Due to the difficulty in conducting trials in the setting of a relatively rare condition, well designed multicenter studies (such as registries) using actual classification criteria and standardized tests should be performed in the future to answer all the opened questions regarding management of APS.
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SATURDAY, 17 JUNE 2017

Genomic imprinting and post-translational modifications

SP0154 RATIONALE TO TARGET IMMUNE MEMORY RESIDING IN INFLAMED TISSUES

H.-D. Chang. *German Rheumatism Research Center Berlin, Berlin, Germany*

T helper (Th) lymphocytes play a major role in the regulation of immune responses and are thought to initiate and drive chronic rheumatic inflammation. Memory Th lymphocytes persist in the inflamed tissue and are refractory to therapeutic intervention. In chronic inflammation Th lymphocytes have undergone molecular adaptations, such as the upregulation of Twist1 and the microRNA miR-148a, which are not found in circulating Th lymphocytes, and support the survival of the Th cells within the inflamed tissue. Within the inflamed tissue, the Th lymphocytes constantly recruit and activate inflammatory cells, such as monocytes/macrophages and granulocytes through the secretion of particular chemokines and interleukins. The monocytes/macrophages in turn can recruit more Th cells into the inflamed tissue. Disrupting this vicious circle by specifically targeting the memory Th cells resident in the inflamed tissue by interfering with their molecular adaptations could be an interesting therapeutic option.
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SP0155 THE ROLE OF POST-TRANSLATIONAL MODIFICATION AND AUTOREACTIVITY

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Rheumatoid arthritis (RA) is a prototype autoimmune disease, with the hallmark signs of synovial inflammation and the presence of autoantibodies. Of the different autoantibody systems present in RA, rheumatoid factors (RF) are probably the best studied. Their presence was first detected >70 years and it was in the late 1950s when it was realized that RF reacted to gamma globulins. Since the discovery of RF several other autoantibody systems have been discovered in RA, many of them directed against post-translationally modified protein antigens. The most prominent example of such autoantibodies are anti-citrullinated protein antibodies (ACPA), which are directed against a wide-array of citrullinated proteins. Now RF and ACPA determination are the two major diagnostic laboratory tests for RA and part of the EULAR and ACR criteria for RA.
In the past few years, it has become clear that the autoantibody response present in RA extends towards several other modified proteins, such as proteins modified by acetylation or carbamylation. As all these auto-antibodies recognize Post-Translationally Modified (PTM) proteins, these antibodies are collectively called Anti-Modified Protein Antibodies (AMPA). In the context of this presentation, I will focus on the auto-antibody response against citrullinated, carbamylated and acetylated proteins.
Carbamylation leads to the formation of homocitrulline. Structurally, homocitrulline greatly resembles citrulline but is one methylene group longer. Citrulline is generated when PAD enzymes modify the amino acid arginine. In contrast, the amino acid homocitrulline is generated by a chemical reaction in which cyanate reacts with the amino acid lysine. Arginine and lysine are located at different positions in the amino acid sequence of proteins, and therefore these modifications occur at different positions in proteins with different flanking amino acids. Intriguingly, although homocitrulline residues can also be recognised by auto-antibodies, these auto-antibodies often do not crossreact with citrulline. Acetylation is a process where acetyl groups are added to free amines of lysine residues by acetyl transferases. Acetylated lysine does not resemble citrulline but bears similarity to homocitrulline except at the side chain terminal amine, which is replaced by a methyl moiety.
By now it is clear that AMPA consist of different auto-antibody families that are largely distinct, but that can also display a certain degree of cross-reactivity. Therefore, the notion is emerging that, although cross-reactivity exist, different classes of AMPAs are generally seen as distinct auto-antibody families that target different antigens, but intriguingly often co-occur. As the AMPA-responses in RA are often found together, it indicates that –somehow- AMPA-reactivity has a commonality that is currently not understood.
Although, the reason why an immune response starts against PTM proteins is not known, it appears crucial to obtain understanding on the breach of tolerance towards PTM proteins as the immune response against these proteins has been intimately implicated in disease-pathogenesis. Understanding the full AMPA response, the triggers that drive AMPA production, their mutual crosstalk and the pathways by which AMPA and/or AMPA-expressing B cells possibly contribute to RA will be important for the development of curative interventions in RA. In the context of this presentation, some of these aspects will be discussed.
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