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Selected sessions on immune tolerance and autoimmune disease

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Immune Tolerance and Autoimmune Disease Cambridge, UK, 26–27 April 2012

The recent Immune Tolerance and Autoimmune Disease conference was held at Emmanuel College Cambridge and organized in collaboration with Anne Cooke (Cambridge University, UK). The smoothly run and well-planned program allowed international experts, academics and scientists to share and discuss recent developments in the understanding of the basic mechanisms of immune tolerance, factors governing autoimmunity, mediators of autoimmunity and pathogenesis as well as strategies for therapeutic intervention. This report outlines some of the highlights from the first day of the conference.

KEYWORDS: autoimmunity • JIA • mTEC • pathogenesis • SLE • T1DM • tolerance

Following a welcome from Anne Cooke (Cambridge University, UK), who had helped to organize a conference featuring a variety of both complementary and diverse presentations, Ludger Klein (University of Munich, Germany) began by discussing his recent work on thymic epithelial cells and their role in central T-cell tolerance. He hypothesized that medullary thymic epithelial cells (mTECs) and dendritic cells (DCs) cooperate to induce CD4 tolerance. Klein elaborated on his group's work investigating the occurrence of exogenous versus endogenous MHC II loading in thymic DCs versus mTECs, respectively.

Through genetic manipulation of mTECs *in vivo*, Klein's group demonstrated that mTECs are relatively 'blind' to their environment and, in addition to both acting as a putative antigen reservoir of tissue-restricted antigens and transferring self-antigens for presentation by thymic DCs, they are able to use an endogenous MHC II loading pathway to act as antigen-presenting cells themselves. This group suggested that these two pathways may work in parallel to induce tolerance [1], with thymic DCs presenting serum-borne antigens and mTECs presenting endogenous self-antigens. They plan to continue the investigation on both the underlying mechanisms and whether they contribute to distinct modes of central tolerance.

Gretel Nusspaumer (University of Basel, Switzerland) also presented work on mTECs in

her presentation 'On the consequences of *in vivo* ablation of Aire-expressing mTECs.' She elaborated on her group's findings that mature mTECs play an essential role in shaping the overall cellular composition of the thymus medulla and inducing central tolerance beyond their role in promiscuous gene expression.

A number of talks throughout the day considered systemic lupus erythematosus (SLE), a complex and heterogeneous autoimmune disease and discussed it in the context of breakdown of tolerance, links with other inflammatory disorders and therapy.

Wei Cao (University of Texas MD Anderson Cancer Center, TX, USA) built on her group's previous finding that amyloid precursor proteins readily form amyloid fibrils in the presence of nucleic acids and described how these fibrils can potentially activate plasmacytoid DCs and enable interferon production to self-DNA, self-RNA and dead cell debris in an FC-receptor independent manner. This could potentially go some way to outlining how, in the absence of autoreactive B cells, abnormal interferon production could be established and lead to a breakdown of tolerance and the instigation of autoimmunity.

The discussion on lupus was continued by Marina Botto (Imperial College London, UK), who reminded the audience that patients with SLE are at a particularly high risk for myocardial infarction and that the mechanisms for this

are currently unknown. She outlined her group's research into a potential synergistic role between SLE and atherosclerosis that could be mediated by the complement system.

Marck Shlomchik (Yale University School of Medicine, CT, USA) gave a presentation that covered 'The beginning of the end? DCs as therapeutic targets in SLE,' in which he outlined his group's view that DCs are an interesting new target for SLE based on how they fit into the scheme of lupus promotion and regulation. He touched on the controversial subject of the efficacy of B-cell depleting agents such as rituximab and belimumab and suggested that targeting DCs might be a suitable alternative approach in lupus treatment as DCs appear to be critical in promoting activation in tissues, for example, in the kidneys where they promote glomerular and interstitial nephritis.

Fiona Powrie (Oxford University, UK) gave a well-received presentation on 'Gut reactions: immune pathways that control intestinal homeostasis' in which she highlighted the prevalence of inflammatory bowel disease and the need to better understand the immune pathogenic mechanisms. She outlined her group's recent investigations into the role of Treg cells in controlling intestinal inflammation through IL-10 production and explained that her future research may look to outline ways in which different bacteria promote Tregs and IL-10-producing cells versus Th17 cells and the mechanisms involved in this 'host-microbial handshake.'

Continuing on in the vein of intestinal inflammation, Arno Hänninen (University of Turku, Finland) gave an interesting presentation on the use of imaging to analyze the gut of nonobese diabetic mice fed different diets in order to identify the part of the gut showing inflammation. The results from his team demonstrated that nonobese diabetic mice show a diet-dependent increase in ROS production in the distal ileum, but that this inflammatory activity is not correlated with individual differences in gut permeability or with an apparent development of diabetes. He highlighted the need for further research to examine whether inflammation in the small intestine is related to islet autoimmunity and noted that the inflammation was linked to a diabetogenic diet.

Agnes Lehuen (Paris Descartes University, France) also discussed diabetes and presented her group's research on the role of invariant natural killer T cells in cooperating with plasmacytoid DC and Treg cells during virus infection to prevent both spontaneous and virus-induced diabetes. She called for an investigation into the potential of iNKT cells as cellular targets for the prevention of Type 1 diabetes mellitus (T1DM) in humans.

In addition, Susanna Cardell (University of Gothenburg, Sweden) also discussed T1DM development, but focused on the tolerization of diabetogenic CD4⁺ T cells. She outlined her group's research using a CTA1R7K-DD adjuvant containing a type II collagen peptide to ameliorate both collagen-induced arthritis in mice and to purportedly induce specific CD4⁺ Treg cells preventing T1DM development.

Moving the audience on to the topic of rheumatic disease, Claudia Mauri (University College London, UK) presented on regulatory B cells in health and rheumatic disease with a particular focus on what she termed a 'neglected' area of B-cell research; specifically their division into different subsets. She discussed her team's work on the role of regulatory B cells (Bregs) in the suppression of proinflammatory responses and the maintenance of Tregs. Mauri outlined her group's current theory that Bregs restrain inflammation via IL-10 production through promoting differentiation of immunoregulatory over proinflammatory T cells and thus maintaining tolerance [2]. In addition, she noted that Bregs are numerically reduced in the peripheral blood of patients with active rheumatoid arthritis but that these re-occur in remission, further highlighting the therapeutic potential of this subset in rheumatological disorders.

Lucy Wedderburn (University College London Institute of Child Health and Great Ormond Street Hospital, London, UK) also discussed arthritis, with a focus on gene expression and immunological features in juvenile idiopathic arthritis. She discussed the range of clinical phenotypes observable in this disease and gave insights into her data from a cohort of 35 children, which indicates that there is a pivotal balance in T-helper subsets that is set prior to severely apparent or developed clinical features and also that this correlates with disease severity. She also outlined her group's findings regarding the plasticity of T-helper cells at sites of inflammation and outlined well the potential impact that this discovery will have on considerations for therapeutic intervention.

Janine Gotot (Uniklinikum Bonn, Germany) concluded the day's presentations after describing findings involving the suppression of antigen-specific B cells via PD-1. She described a peripheral B-cell tolerance mechanism against tissue antigens seen from *in vivo* findings in which antigen-specific Tregs suppressed autoreactive B cells in mice.

Following the days absorbing lectures, delegates were treated to a drinks reception and the presentation of an array of well-prepared posters, produced by both speakers and talented members of their groups. The conference continued on 27 April, with presentations on mediators of autoimmunity/pathogenesis and strategies for therapeutic intervention.

Following on from this successful conference, Abcam will be sponsoring a conference on the topic of 'Inflammation and Atherosclerosis' to be held at Munich, Germany (20–21 September, 2012) [101].

Financial & competing interests disclosure

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