

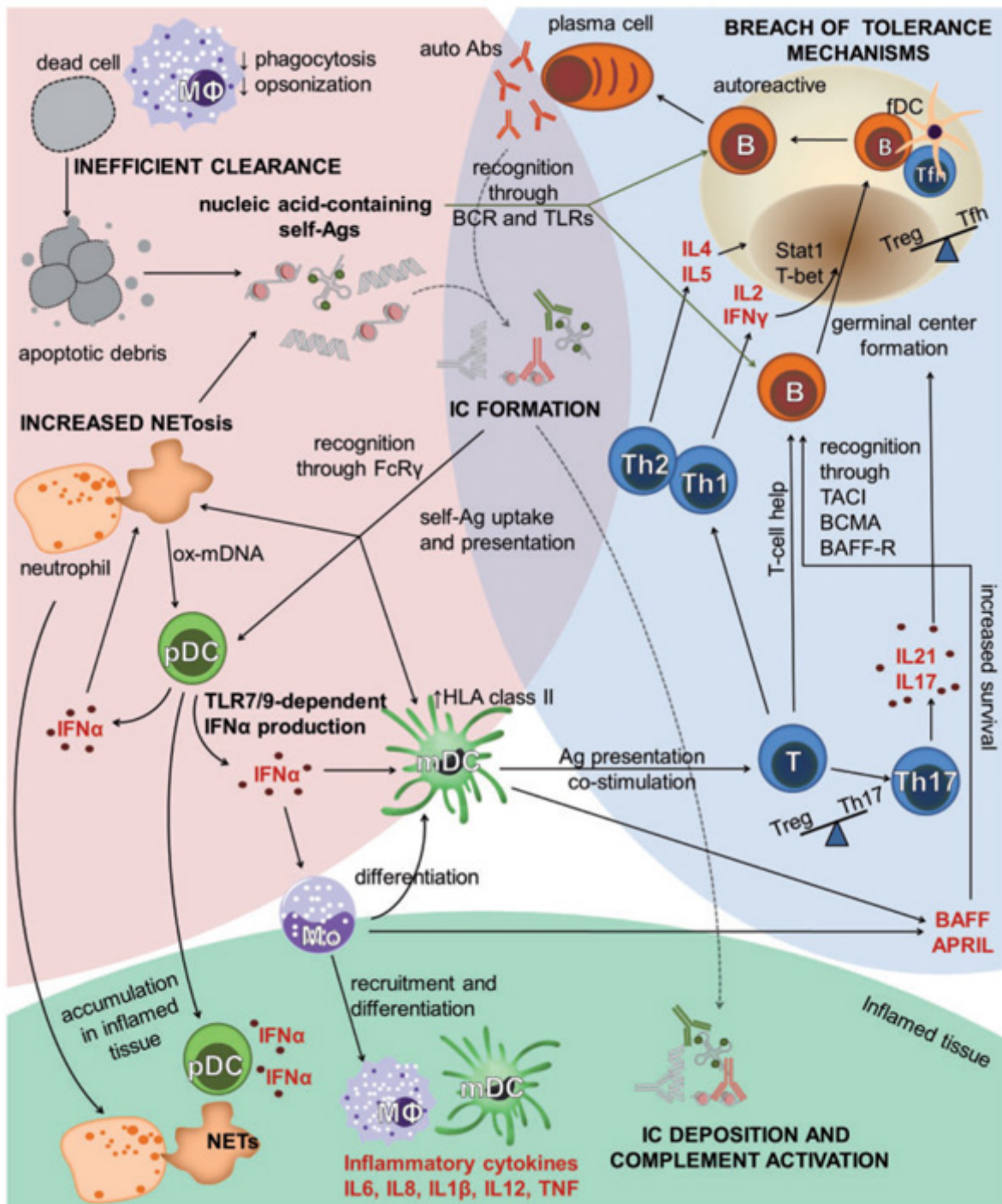
Research

Research Focus

The global increase in the frequency of autoimmune diseases together with the emerging autoimmune-related side effects of cancer immunotherapy have led to a need for further understandings in breaches of tolerance and immune activation. Our research is focused on the mechanisms that maintain the balance of the immune system. Innate immune mechanisms are fundamental for an effective host response to potentially pathogenic organisms. However, dysregulation can result in susceptibility to infections or pathogenic inflammation and autoimmunity. Much of our work to date has focused on the roles of the endosomal innate toll-like receptors (TLR) in the regulation of the immune response in the archetypal autoimmune disease, systemic lupus erythematosus (SLE). This is a systemic immunological disease whereby the host's immune system develops reactivity to self, resulting in systemic inflammation and often, kidney disease. The mainstay of therapy since the 1950s has been non-specific immunosuppressants. While these are effective at treating symptoms and tissue manifestations of autoimmune diseases, their non-selective nature also causes broad toxicity profiles.

We are a translational lab, working with multiple animal models and clinical human samples to understand mechanisms leading to systemic autoimmunity so we can improve therapeutic interventions.

• Projects



Credit: Rheumatology (Oxford). 2017 Apr 1;56(suppl_1):i55-i66. doi: 10.1093/rheumatology/kew427. Pathways leading to an immunological disease: systemic lupus erythematosus. Zharkova O *et al.* (Open Access)

The Fairhurst lab is working to ascertain how the immune system maintains an effective balance between protection from infections, cancer and autoimmunity. By studying the archetypical systemic immunological disease SLE, we can understand crucial mechanisms of immune tolerance and inflammation that are targets for therapy across multiple diseases. We have multiple projects in the scheme presented in the image above (taken from Rheumatology, 2017). Listed here are a few of the main projects led by our research team.

1. Understanding how TLR9 regulates B cell immunity and conventional dendritic cell (DC) activation

TLR9 is an innate intracellular receptor that recognises dsDNA. Historically, the presence of autoantibodies to dsDNA, made this receptor a prime candidate for therapeutic intervention in SLE. Stimulation of B cells with dsDNA immune complexes results in B cell and DC activation and *in vivo* administration of CpG resulted in an increase in autoimmune phenotypes in lupus models. However, surprisingly, genetic ablation of TLR9 did not eliminate autoimmunity, but resulted in an augmentation in lupus-like phenotypes. The mechanisms by which TLR9 maintains tolerance are as yet unknown. We have generated B6.*Sle1*TLR9^{-/-} mice which develop similar phenotypes to mouse models of other strains (MRL / Nba2). We are assessing the impact of TLR9 on B cell function and in cDCs.

2. Determining the mechanism by which TLR7 modulates immune activation.

The innate immune Toll-like receptor (TLR) family has been shown to play a fundamental role in promoting pathogenesis. Multiple investigations have shown that the ssRNA receptor, TLR7 and its downstream MyD88 signaling pathway are critical for the initiation of autoimmunity and development of self-reactivity (reviewed in: Fairhurst 2006; PMID17145301). In TLR7-sufficient autoimmune prone systems an additional increase in TLR7 results in severe autoimmune phenotypes. The Fairhurst lab has shown that a 2-fold increase in TLR7 alone on the *Sle1* background is sufficient to drive disease using a novel low copy conditional TLR7 BAC transgenic system (*Sle1*Tg7loxP, aka *Sle1*Tg7) (Hwang 2012; PMID23150717). We have shown that TLR7 upregulation specifically in cDCs is required for the progression to severe disease (Celhar 2015; PMID26512111). We are currently assessing downstream signalling molecules in the TLR7-signaling pathway, and determining the impact of disease on TLR7 protein expression across multiple leukocyte lineages and tissues.

3. Assessing the impact of the microbiome on systemic immunological activation

The intestinal microbiota plays an important role in the development and regulation of both innate and adaptive immunity. Several studies have suggested that the development of a number of autoimmune diseases, including RA, T1D and EAE, are influenced by gut microbiota. However, investigations into the role of the microbiota in the development of SLE

are unknown. TLR9 is expressed on the surface of intestinal epithelial cells, may play an important role in the development of disease. We are working on understanding whether the microbiome influences systemic inflammation and autoimmunity in TLR9-deficient non autoimmune and autoimmune *Sle1* mice.

4. Examining the loss of immune tolerance through SLAMF polymorphisms.

Multiple murine studies have demonstrated that a small region on chromosome 1 is fundamental for the development of disease (termed *Sle1*, *MRLc1*, *Nba2*, *Sbw1*, *Lbw7*, *Cgnz1*, *Bxs1* and *Bxs2*). When present on a non-autoimmune prone B6 background, the NZW-derived locus (B6.*Sle1*) confers a loss of tolerance to nuclear material resulting in a high penetrance of antinuclear antibodies (ANAs), and an increase in B and T cell activation. It is now evident that polymorphisms of the signaling lymphocyte activation molecule family (SLAMF) are responsible for these mild autoimmune traits. Further, recent studies have supported a role for both Ly108 and CD84 in this model system. We are assessing the impact of *Sle1*-derived and B6-derived SLAMF members in the loss of tolerance and modulation of the immune response.

5. Modulation of T cell functions for immune therapies

Our observations indicate fundamental defects in the CD4+ repertoire in SLE, including regulatory cells. We propose that these are opposite to the events occurring in cancer. We have generated a series of murine models with the *Sle1/Sle1*TLR9 background to dissect the mechanisms of immune tolerance to assess novel targets for therapy.