Toll-Like Receptor (TLR)-7 Plays A Critical Role In Regulation Of Systemic Immunity

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Abstract
The innate toll like receptor (TLR)-7 plays a primary role in immune recognition of the virus and the host response. In murine systems and in patient populations, TLR7 upregulation has been associated with severe inflammation and autoimmunity, particularly with regard to systemic lupus erythematosus (SLE). The incidence of SLE is 1 in 50-2000, with the large range attributed to a number of factors including under-diagnoses and ethnicity differences. It is more frequent and severe in Chinese and African American ethnicities. Owing to the complex aetiology and heterogeneity of autoimmunity, murine models have provided a particularly useful tool to analyse mechanisms of disease progression. Their value has been proven repeatedly with pre-clinical trials which have proven efficacy in clinical disease.

TLR7 is an intracellular receptor located on the endosome, recognising single stranded RNA (ssRNA). Ligation with viral ssRNA initiates downstream activation of signaling molecules resulting in activation of NF-kB or IFN-regulatory factor (IRF)-7, through a MyD88-dependent cascade resulting in the production of pro-inflammatory cytokines or IFNa respectively. The yaa locus is a murine lupus susceptibility region dependent on the translocation of TLR7 which results in a 2-fold upregulation of expression and function. To ascertain whether this upregulation was necessary for the systemic inflammation we developed a novel low copy conditional TLR7 BAC transgenic mouse strain (Tg7). We have shown that a 2-fold upregulation of TLR7 on the Sle1 background is sufficient for the development of severe nephritis and associated severe autoimmune traits. Furthermore, that this upregulation is critical within the CD11c+ DC. In parallel studies, we determined a requirement for TLR7 for mild autoimmune traits in the Sle1 system. In addition, we determined that the receptor is necessary for normal circulating IgM and IgG levels in aged wild type mice. Thus TLR7, plays a critical role in the homoeostasis of the immune system.

About the speaker
Anna-Marie Fairhurst received her PhD in Immunology/Pharmacology at the William Harvey Research Institute at St Bartholomew’s Hospital, University of London in 2002. During her PhD she examined the roles of neutrophil-FcγRIIb and tristetraprolin (TTP) expression in rheumatoid arthritis under the direction of Nicolas Goulding and Paul Wallace (Dartmouth, NH). From London she moved to the NIH, in Bethesda, Maryland, USA to undertake a postdoc with Peter Lipsky. Projects were focused on the mechanisms of the initiation and progression of autoimmunity. Her main directions were to examine innate regulation of systemic lupus erythematosus (SLE) and the effects of IL-21 on B cell transcription factors. In the Spring of 2004, she moved to Dallas, TX, to continue studying SLE with Ward Wakeland. Her research focused on the genetic and immunological mechanisms which drive SLE pathogenesis using multiple murine models, specifically examining the role of IFNα and the TLRs.
In 2008, Anna-Marie became an Assistant Professor in the Department of Immunology at UT Southwestern Medical Center at Dallas. She joined SIgN in March 2010. The research of the Fairhurst lab is focused on innate immune pathways, together with activators and regulators of these systems. 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 the work to date has focused on the roles of the endosomal innate toll-like receptors (TLR) in the regulation of the immune response.