

A133 BREAKAGE OF B CELL TOLERANCE BY ANTIGENS ON FOLLICULAR DENDRITIC CELLS

Mohey Eldin El Shikh,¹ Rania M El Sayed,¹ Maciej Kmiecik,^{2,3} Masoud Manjili,^{2,3} Andras Szakal,⁴ Costantino Pitzalis,¹ John Tew² ¹*Experimental Medicine & Rheumatology, William Harvey Research Institute, Barts and The London School of Medicine, Queen Mary University of London, London, UK;* ²*Microbiology and Immunology;* ³*Massey Cancer Centre;* ⁴*Anatomy and Neurobiology, VCU School of Medicine, Virginia Commonwealth University, Richmond, Virginia, USA*

10.1136/ard.2010.148999.9

Background and objectives Autoimmune disorders frequently display autoreactive germinal centres (GCs) with immune complex (IC)-bearing follicular dendritic cells (FDCs) suggesting that FDCs are involved in the pathogenesis of autoimmune diseases. The authors recently described induction of T cell-independent (TI) antibody (Ab) responses to T dependent (TD) antigens (Ags) by presenting the TD Ags on FDCs. Rather than presenting peptide fragments, FDCs multimerize monomeric Ags by trapping them in ICs via FDC-FcγRIIB and then present them polyvalently with a characteristic periodic spacing between epitopes of 200–500 Å. This allows extensive B cell receptor (BCR) cross-linking that induces TI B cell activation, GC formation, and Ag-specific Ig secretion in less than 48 h in the presence of FDC-derived co-stimulatory signals. These correlations prompted the hypothesis that multimerized self/neo-Ags on FDCs would break B cell tolerance; induce autoreactive GC formation, and auto-Ab responses.

Materials and methods ICs of autologous tumour necrosis factor α or IgE, were injected into BALB/c mice. In addition, soluble hen egg lysozyme transgenic (sHEL-Tg) and rat *neu*-Tg FVBN202 mice were challenged with HEL or the subdomain II of the extracellular domain of rat *neu* (ECDII), respectively, in the form of ICs. These auto/neo Ags were selected because Abs reactive with these Ags are used clinically or, in the case of sHEL-Tg mice, the profound tolerance to sHEL has been well verified.

Results Remarkably, in all cases, the ICs were trapped by FDCs; and autoreactive GCs, plasmablast differentiation and strong auto-Ab responses were induced within 48 h. In marked contrast, free Ag that would have unfettered access to BCRs did not load on FDCs and did not induce detectable auto-Abs.

Conclusions This is the first report of deliberately inducing auto-Abs by self/neo-Ags on FDCs. The data provide a mechanism by which FDCs may contribute to autoimmunity, and suggest a novel approach for targeting mediators of chronic inflammation, hypersensitivity and cancer. Therapeutic induction of auto-Abs by FDC-ICs may provide self-regulated high affinity Abs efficient in long-term disease control.