

maintenance and regulation of autoreactive GCs and auto-antibody (Ab) production has not been analysed. The authors hypothesised that auto-immune complex (IC) retention on FDCs critically regulates auto-Ab production and that FDC-IC unloading would significantly inhibit auto-Ab levels.

Materials and methods To test our hypothesis, purified human FDCs, B cells, T cells, complement, fibrinogen (Fib) and anti-Fib from high anti-citrullinated peptide protein Ab (ACPA) sera were used to set up controlled in vitro autoreactive GC reactions. The reactions were differentially reconstituted by the cellular and molecular components of GCs. The immunoglobulin G (IgG) specific Endoglycosidase S (EndoS) was used to inhibit Fib-IC retention on FDCs and Fib-specific auto-Ab production. Moreover, the ability of IC retention on FDCs to break B cell tolerance and induce auto-Ab production in tolerant animal models was verified.

Results Our in vitro studies indicated that: (1) In the presence of Fib-IC loaded FDCs alone, significant amounts of Fib-specific IgM are produced; (2) In the presence of FDCs alone or T cells alone, Fib-specific IgG is insignificant; (3) The co-stimulatory effect of both FDCs and T cells is required for induction of significantly high levels of Fib-specific IgG; (4) EndoS significantly inhibited Fib-specific IgG production in FDC-T cell-assisted cultures via mechanisms involving interference with FDC-IC retention, inhibition of complement activation, and, possibly, IgG B cell receptor deglycosylation.

In vivo, FDC-ICs induced autoreactive GCs and auto-Ab production in well-characterised animal models tolerant to hen egg lysozyme (HEL) as well as targets of therapeutic importance including TNF- α , IgE, and the extracellular domain two of the neu antigen (ECDII). However, safe termination of these induced auto-Ab responses was challenged by the non specific activity of EndoS as indicated by its inhibitory effect on protective immune responses to the foreign antigen ovalbumin (OVA). To avoid the non-selective activity of EndoS, the authors designed bait and pray 'Split-EndoS conditional re-functionalisation' system that selectively deglycosylates target Abs (pray) engaging their antigens (baits) on the EndoS molecules. The system was successfully tested as indicated by the ability of biotin-baited EndoS to selectively deglycosylate anti-biotin IgG.

Conclusion This is the first report analysing the critical role of FDC-ICs in auto-Ab production in in vitro autoreactive germinal centre reactions, with potential therapeutic targeting of clinically important antigens and safe termination using EndoS.

15 REGULATION OF AUTO-ANTIBODY PRODUCTION BY PERSISTING AUTO-IMMUNE COMPLEXES ON FOLLICULAR DENDRITIC CELLS

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Background and objectives Follicular dendritic cells (FDCs) are characteristic components of organised tertiary lymphoid structures (TLS) containing germinal centres (GCs) in chronically inflamed tissues. However, the role of FDCs in initiation,