

Plasmacytoid dendritic cells and immunoglobulin class switching with

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How can plasmacytoid dendritic cells influence immunoglobulin heavy chain class switching?

Andrea Cerutti: By substituting the heavy chain constant region (C_H) of IgM and IgD with that of IgG, IgA or IgE, class switching endows antibodies with novel effector functions that enhance antigen clearance. Most antigens trigger class switching in the germinal center of lymphoid follicles by inducing $CD4^+$ T cells to express CD40L (1). Although capable of generating protective IgG, IgA and IgE with high affinity for antigen, this T cell-dependent (TD) pathway requires five to seven days, which is too much of a delay to neutralize quickly replicating pathogens.

To compensate for this limitation, extrafollicular B cells, including splenic marginal zone and mucosal B cells, rapidly undergo T cell-independent (TI) production of low-affinity IgM, IgG and IgA in response to microbial polysaccharides, LPS, CpG DNA, RNA, etc. (2). In the presence of these highly conserved pathogen-associated molecular patterns, plasmacytoid dendritic cells release IFN- α and INF- β (IFN- α/β), which in turn stimulate myeloid dendritic cells to up-regulate innate class switch-inducing molecules structurally related to CD40L (3).

What is the role of interferon?

Andrea Cerutti: Plasmacytoid dendritic cells release IFN- α/β upon sensing microbial molecular patterns through TLRs (4). IFN- α/β regulates antibody production through at least two mechanisms. In the first mechanism, IFN- α/β stimulates IgM production and class switching by inducing myeloid dendritic cells to up-regulate B cell-acti-

vating factor of the TNF family (BAFF, also known as BlyS) and its homologue a proliferation-inducing ligand (APRIL) (3). In the second mechanism, IFN- α/β cooperates with IL-6, another dendritic cell-derived cytokine, to stimulate the differentiation of class-switched B cells into antibody-secreting plasma cells (5-7).

Are BAFF and APRIL involved?

Andrea Cerutti: Innate immune cells constitutively release soluble BAFF and APRIL in the extracellular environment (8). Soluble BAFF and APRIL provide a tonic signal that is essential for the survival of peripheral B cells and bone marrow plasma cells (8, 9, 10). In the presence

of microbial products or IFN- α/β , innate immune cells up-regulate membrane-bound and soluble BAFF and APRIL, thereby enabling antigen-stimulated B cells to undergo CD40-independent IgM secretion and class switching (3).

What is known about the different pathways leading to immunoglobulin class switching?

Andrea Cerutti: Class switching is guided by intronic switch DNA regions located upstream of each C_μ , C_γ , C_α and C_ϵ and occurs through class switch DNA recombination (CSR) (1). CSR is preceded by germline CH gene transcription and requires activation-induced cytidine deaminase (AID) (2, 11). This B cell-specific enzyme is recruited to actively transcribed switch regions and promotes CSR by introducing double-strand DNA breaks within these regions. TD antigens stimulate germline CH gene transcription and AID expression through an NF- κ B-dependent signal provided by CD40L and a STAT- or Smad-dependent signal provided by a T cell-derived cyto-

kine (1, 11). The second signal is necessary to target a specific CH gene. For example, IL-4 triggers C_γ and C_ϵ transcription through STAT6, whereas TGF- β triggers C_α transcription through Smad. Similarly to TD antigens, TI antigens induce germline transcription, AID expression and CSR by utilizing an NF- κ B-dependent signal provided by BAFF, APRIL or a TLR ligand and a second STAT- or Smad-dependent signal provided by a cytokine (3, 11-14). Of note, BAFF and APRIL activate NF- κ B by engaging transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), B cell maturation antigen (BCMA) and BAFF receptor (BAFF-R) (3, 8, 15).

Are your findings useful for the development of therapies for antibody-mediated autoimmune disorders?

Andrea Cerutti: Our findings show that B cells can initiate IgH class switching through a CD40-independent pathway that involves BAFF and APRIL (3, 12, 14). In addition, our data indicate that B cells can undergo TI class switching upon activation by CpG DNA through a TLR9-dependent pathway that cooperates with IL-10 and BCR engagement (13, 14). Although conferring greater flexibility to B cells, all these TI pathways can have an autoimmune downside. Consistent with this, certain antibody-mediated autoimmune disorders, such as lupus, are associated with dysregulated IFN- α and BAFF production, which possibly results from continuous activation of plasmacytoid dendritic cells by CpG-rich chromatin released by dying

autologous cells (7, 16-18). In light of our and other results (3, 12, 15), we propose that autoreactive B cells can undergo pathogenic IgG and IgA class switching upon engagement of TACI and BAFF-R by BAFF and APRIL. Pathogenic class switching could also involve dual TLR9 and BCR engagement by endogenous CpG DNA (13, 16, 17). This implies that TACI and BAFF-R signaling inhibitors (e.g. TACI-Ig, BCMA-Ig, blocking antibodies to BAFF and APRIL) as well as TLR inhibitors (e.g. inhibitory CpG oligonucleotides, chloroquine-related compounds) may be able to attenuate the clinical manifestations of autoimmune disorders by interfering with the production of highly pathogenic class-switched antibodies.

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