Plasmacytoid DCs Induce Gutsy Plasma Cells

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Immunoglobulin (Ig) A is critical for protective immune responses at mucosal surfaces. In this issue of *Immunity*, Tezuka et al. (2011) identify an important relay between stromal cells and plasmacytoid dendritic cells that regulates IgA production by murine B cells.

B cells have the capacity to undergo class switch recombination (CSR) allowing them to secrete multiple classes of immunoglobulin (Ig) isotypes. This represents one mechanism of Ig diversification whereby B cells alter the effector function of their antibody (Ab) products without modifying Ag specificity. Each of these Ig classes have preferential roles in immune responses depending on their site of generation and nature of the antigenic stimulus. Thus, IgG is produced systemically and comprises most of the Ig in serum and extravascular compartments where it predominantly functions in antiviral and antibacterial immunity. In contrast, IgE exists at extremely low concentrations in serum but is produced in response to parasitic infections, as well as allergens, whereas IgA is secreted predominantly in mucosal tissues and represents the majority of Ig in these sites (Cerutti et al., 2010).

CSR can occur via T cell-dependent (TD) and T cell-independent (TI) mechanisms. TD CSR typically requires the integration of signals provided by cognate $CD4^+$ T cells in the form of CD40 ligand (CD40L) interacting with CD40 on B cells in a cell contact-dependent manner and a soluble cytokine. Whereas CD40L primes B cells to switch to all Ig isotypes, TGF-β is considered to be the obligatory cytokine required for the majority of IgA produced by human and murine B cells (Cerutti et al., 2010; Tangye et al., 2006). The TI pathway for CSR to IgA involves signaling through Toll-like receptors (TLRs) as well as the cytokines BAFF and APRIL, which are produced by many cell types including hematopoietic and nonhematopoietic cells (Cerutti et al., 2010; Tangye et al., 2006). However, BAFF and APRIL can also induce CSR in the presence of appropriate T cell-derived cytokines—TGF-β for IgA—albeit in a CD40L-independent manner (Cerutti et al., 2010). Thus, these cytokines can contribute to both TD and TI CSR. Interestingly, there appears to be a "division of labor" between the function of IgA produced by TD and TI pathways whereby high-affinity IgA generated during TD responses is important for neutralization and clearance of pathogenic microorganisms, whereas low-affinity IgA arising from TI responses maintains commensal bacteria-dependent homeostasis within the gut (Cerutti et al., 2010). An issue that has not been completely resolved, however, is the contribution of dendritic cell (DC) subsets to IgA production. This is the subject of the paper by Tezuka et al. (2011) in this issue of *Immunity*.

The partitioning of IgA responses to mucosal associated lymphoid tissues (MALT) appears inconsistent with the systemic production of BAFF, APRIL, CD40L, and TGF-β by numerous cell types present throughout all lymphoid tissues. Consequently, several studies have addressed the questions of (1) why B cells preferentially switch to IgA in MALT and (2) why IgA^+ B cells are retained at these sites. The answer to both of these questions appears to depend on the function of (DCs) located in mucosal tissues. First, DCs from Peyer's patches (PP) were found to be distinct from those in spleen or lymph nodes (LN) inasmuch that PP, but not splenic or LN, DCs were potent inducers of large quantities of IgA by B cells (Massacand et al., 2008; Mora et al., 2006; Sato et al., 2003). One of the mediators responsible for this effect of MALT-derived DCs is retinoic acid (RA) (Massacand et al., 2008; Mora et al., 2006; Uematsu et al., 2008). Indeed, exogenous RA converts splenic DCs into potent helpers for IgA secretion by cocultured human and murine B cells (Mora et al., 2006; Uematsu et al., 2008). Second, the tropism of IgA^+ cells for MALT reflects the conditioning of these cells by DCs during mucosal responses. Specifically, RA imprints upon IgA-secreting B cells expression of CCR9 and α4β7 (Mora et al., 2006), characteristic gut-homing receptors that attract and/or retain cells in the MALT by rendering them responsive to the chemokine CCL28 and the adhesion molecule MadCAM-1, both of which are highly expressed in mucosal tissues.

Because many subsets of conventional DCs exist, attempts have been made to identify the population of MALT DCs responsible for inducing IgA secretion. Both a $CD11c^{lo}$ TNF+iNOS-producing (Tip) (Tezuka et al., 2007) and a $CD11c^{hi}CD11b^{hi}$ (Uematsu et al., 2008) DC subset have been attributed to have the ability of regulating IgA production in MALT (Figure 1). Despite these insights, the mechanisms underlying DC-mediated IgA secretion are not only complex, but incompletely resolved. For instance, the effects of the Tip-DC subset on TD IgA CSR relied on induction of TGF-βRIII on B cells by nitric oxide (NO), whereas they regulated TI IgA secretion in a BAFF- and APRIL-dependent manner that required endogenous iNOS expression. Furthermore, iNOS expression by Tip-DCs required MyD88 signaling downstream of TLR2, TLR4, and/or TLR9 (Figure 1, top; Tezuka et al., 2007). The activation requirements of $CD11c^{hi}CD11b^{hi}$ DCs differed from Tip-DCs. Thus, RA production by $CD11c^{hi}CD11b^{hi}$ DCs was necessary to induce TI IgA secretion (Massacand et al., 2008; Uematsu et al., 2008), and this depended exclusively on signaling through TLR5 (Uematsu et al.,

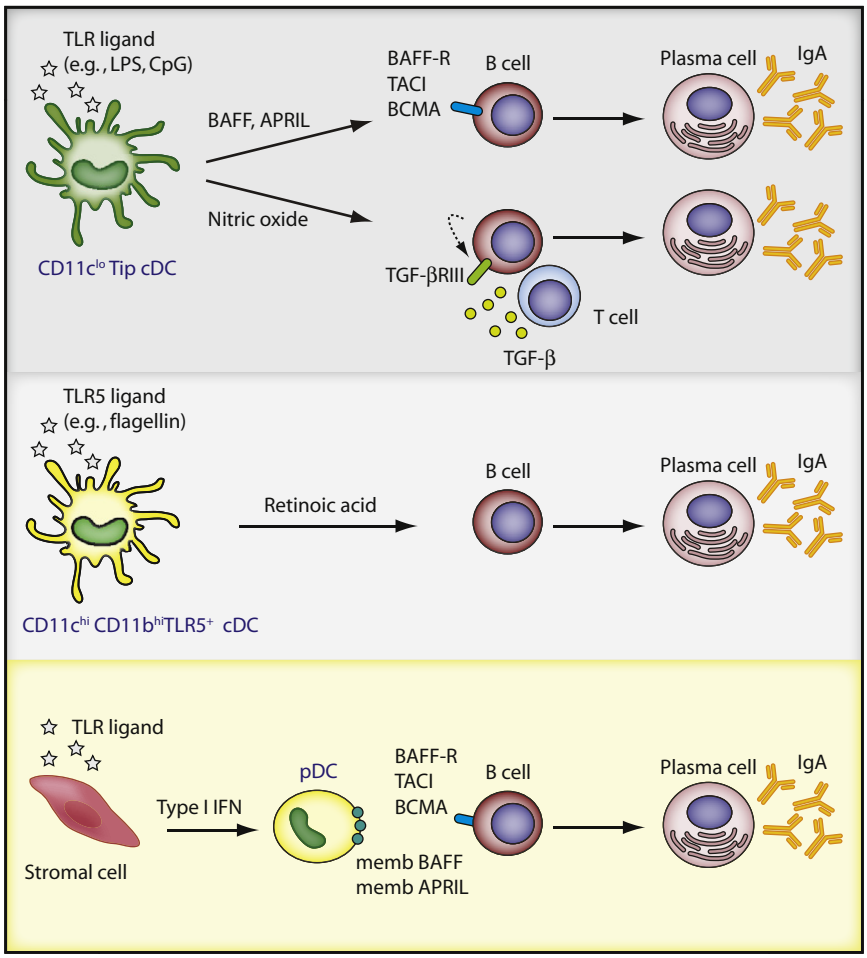

Figure 1. Distinct Mechanisms Underlie the Ability of Different Subsets of Conventional and Plasmacytoid DCs to Regulated IgA Secretion in Mucosal Tissues

$CD11c^{lo}$ TNF and iNOS-producing (Tip) cDCs induce TI and TD IgA production via the secretion of BAFF and APRIL, and nitric oxide (NO), respectively. NO induces expression of TGF-βRIII on B cells, which presumably allows them to respond to $CD4^+$ T cell-derived TGF-β. Production of both BAFF, APRIL, and NO requires TLR stimulation of the cDCs. In contrast, $CD11c^{hi}CD11b^{hi}$ cDCs induce IgA secretion by inducing RA in a TLR5-dependent manner. pDCs, however, express membrane (memb) BAFF and APRIL in response to type I IFNs released by stromal cells after exposure to commensal bacteria. IFN-primed pDCs migrate to B cell areas to induce TI IgA production.

2008) rather than the suite of TLRs necessary for IgA induced by Tip-DCs (Figure 1, bottom; Tezuka et al., 2007). Lastly, IL-6 has been found to be either required (Sato et al., 2003) or dispensable (Mora et al., 2006) for IgA secretion induced by MALT DCs. Thus, mucosal DC subsets appear to be capable of inducing IgA secretion by several mechanisms.

Tezuka et al. (2011) extended these studies by dissecting the role of plasmacytoid DCs (pDCs) in IgA production. A striking observation was that pDCs derived from MALT, including PP and mesenteric LNs (MLN), were more efficient at inducing TI IgA secretion by B cells than were conventional DCs (cDC) isolated from these same sites, or even pDCs from peripheral LNs (PLN). Analysis of both cDCs and pDCs revealed that pDCs from MLN or PP expressed greater amounts of BAFF and APRIL mRNA and produced more IL-6 than corresponding cDCs or PLN pDCs. Consistent with these findings, IgA secretion by B cells cultured with MALT pDCs was reduced dramatically by neutralizing BAFF and APRIL and less so by blocking IL-6. Further examination of interactions between pDCs and B cells demonstrated that membrane-bound BAFF and/or APRIL were necessary for pDCs to induce IgA production. Indeed, BAFF and APRIL were present on the surface of a small but detectable proportion of pDCs but not cDCs. By contrast, no role was found for TGF-β or RA in pDC-induced IgA production (Tezuka et al., 2011).

The final question addressed what the factors were that induced expression of BAFF and APRIL on pDCs. Type I IFNs were a likely candidate because they upregulate BAFF in myeloid cells (Cerutti et al., 2010; Tangye et al., 2006) and enhance Ab responses (Jego et al., 2003). When pDCs were obtained from MLNs of *Ifnar1*-deficient mice, their capacity to induce IgA was impaired; this was a direct consequence of a paucity of BAFF and APRIL in these cells (Tezuka et al., 2011). Although pDCs themselves produce vast quantities of type I IFNs in response to viral stimulation (Jego et al., 2003), the IFN-producing cells responsible for inducing BAFF and APRIL in MALT pDCs were of stromal origin. Notably, the degree of type I IFN expression by stromal cells in PP exceeded that of those in the spleen (Tezuka et al., 2011). This provides a mechanistic basis for the improved efficacy of MALT-derived pDCs in inducing IgA secretion over pDCs from PLN.

Taken together, these findings suggest that under steady-state noninflammatory conditions, interactions between stromal cells and pDCs result in BAFF and APRIL production by pDCs in a type I IFN-dependent manner. These cytokines then act on B cells to induce CSR to, and subsequent secretion of, IgA (Figure 1, bottom). Expression of type I IFNs by stromal cells in PP also required TLR signaling, presumably after exposure to commensal microbes. Collectively, an ongoing dialog between these distinct cell types substantially contributes to TI IgA production, which is important for not only mucosal immunity but also gut homeostasis. Although stromal cells clustered with pDCs and pDCs clustered with B cells, there was little evidence of interactions occurring simultaneously between these three cell types. Thus, a relay needs to be established whereby IFN-primed BAFF- and APRIL-producing pDCs relocate from their position adjacent to stromal cells to one in close proximity with B cells (Figure 1). Although the cues that guide migration of pDCs to B cell follicles are unknown, TLR-stimulated follicular DCs in PP were recently shown

to produce BAFF, APRIL, and CXCL13 as well as molecules that enable TGF-β synthesis that together control IgA secretion in MALT (Suzuki et al., 2010). It would therefore be interesting to determine whether follicular DCs are also involved in this relay by recruiting activated pDCs to B cell follicles to regulate IgA production.

By demonstrating a major role for MALT-resident pDCs, rather than cDCs, in regulating TI IgA responses under steady-state conditions, these findings (Tezuka et al., 2011) add another layer of complexity to the regulation of mucosal IgA responses. In light of other studies (Jego et al., 2003; Massacand et al., 2008; Mora et al., 2006; Sato et al., 2003; Suzuki et al., 2010; Tezuka et al., 2007; Uematsu et al., 2008), it is clear that induction of IgA by DCs differentially depends on TGF-β, IL-6, RA, BAFF, and APRIL, with the requirement for each of these factors reflecting the nature of the DC subset, the inflammatory or quiescent milieu, the availability of T cell help, and the specific location within the MALT (Figure 1). These findings also raise several interesting questions. First, it remains unclear why IgA responses in PP were predominantly TD whereas those in the MLN were TI despite the fact that pDCs and stromal cells isolated from these sites appeared to be functionally similar with respect to expression of elevated amounts of BAFF and APRIL and type I IFNs, respectively, compared to corresponding cells in non-MALT sites (i.e., spleen, PLN). Second, it is unknown whether BAFF, APRIL, or BAFF-APRIL heterodimers or a combination of these molecules is the key mediator of pDC-induced IgA secretion. And lastly, the receptor expressed on B cells that delivers the BAFF and APRIL signal for CSR to IgA in this setting remains to be identified. Although TACI has been implicated in IgA production in vitro (Cerutti et al., 2010; Tangye et al., 2006), it will be important to establish whether this also occurs within MALT and whether an impairment in this pathway contributes to the Ig deficiency in humans with mutations in *TNFRSF13B* (encoding TACI). Although this study by Tezuka et al. (2011) has shed substantial light on the dynamic control of IgA production, answers to these questions will provide a greater understanding of the biology of IgA-mediated immunity during TD and TI responses and potentially reveal strategies for improving such responses in healthy and immunodeficient individuals.

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Standing Guard at the Mucosa

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Most successful vaccines elicit antibodies that protect against infection. In this issue of *Immunity*, Bomsel et al. (2011) show in the rhesus macaque model that vaccine-induced mucosal antibodies, rather than circulating neutralizing antibodies, may be critical components for protective immunity against HIV-1.

Antibodies patrolling the mucosal epithelium can play a crucial role in blocking HIV-1 entry and infection after sexual exposure. Bomsel et al. (2011), in this issue of *Immunity*, report that an HIV-1 gp41 envelope vaccine elicits mucosal antibodies in rhesus macaques that may protect against simian-human chimeric immunodeficiency virus (SHIV) infection after repeated intravaginal low-dose exposures (Bomsel et al., 2011). Protected animals mounted vaginal IgA antibodies, which blocked HIV-1 transcytosis, and IgG antibodies, which mediated antibody-dependent cellular cytotoxicity (ADCC). However, the animals lacked serum neutralizing antibodies. These findings highlight the contribution of diverse effector activities of antibodies in defending against HIV-1 at the portal of entry and raise the question of whether circulating, broadly reactive