Alarming dendritic cells for Th2 induction

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There is an ever-increasing understanding of the mechanisms by which pathogens such as bacteria, viruses, and protozoa activate dendritic cells (DCs) to drive T helper type 1 (Th1) responses, but we know much less about how these cells elicit Th2 responses. This gap in our knowledge puts us at a distinct disadvantage in designing therapeutics for certain immune-mediated diseases. However, progress is being made with the identification of novel endogenous tissue factors that can enhance Th2 induction by DCs.

$CD4^+$ T helper cells represent a diverse and ever-expanding assortment of immune cells, including Th1, Th2, Th3, Th17, and T regulatory (T reg) cells. The last three subsets are relatively new arrivals on the scene, whereas Th1 and Th2 cells have been the focus of intense research since their original definition by Mosmann et al. in the late 1980s (1). Most facets of the $CD4^+$ T cell response—including induction, development, maintenance, effector function, and memory function—are better understood in Th1 cells than in their Th2 counterparts. This can be explained in part by the fact that Th1 cells drive the pathology of many of the most severe and debilitating diseases that affect the developed world. However, Th2 responses are also important, and not simply because of their ability to counterregulate Th1 development. Th2 responses can be beneficial, for example, in protection against helminths. But this type of response may also be severely damaging, such as in fibrotic or allergic disease. It is widely recognized that without a detailed understanding of the specific pathways of differential T helper cell development we cannot determine how best to correct dysregulated immune responses.

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DCs are pivotal in the control of developing immune responses, as they govern both the initiation and polarization of adaptive immunity (2). Although Th1 induction by DCs is relatively well documented and rapid progress is being made on Th17 stimulation (3), there is a glaring deficiency in our understanding of the mechanisms used by DCs to induce and direct Th2 responses. Emerging evidence, particularly from studies on DC responses to helminths (the Th2 experts), suggests that DCs stimulated in Th2 environments tend to flaunt conventional definitions of DC activation. Moreover, Th2-inducing DCs are generated not only in infection but also by exposure to innocuous allergens (4) and, most surprisingly, to endogenous ligands such as the cytokine thymic stromal lymphopoietin (TSLP) (5). In the latter context, a new study from Yang et al. on page 79 of this issue (6) suggests that innate cells can shape adaptive immunity through the release of the antimicrobial protein eosinophil-derived neurotoxin (EDN), a ribonuclease with antiviral properties that can also act as a chemoattractant and activation stimulus for DCs (7).

DC instruction of Th cell differentiation

The current paradigm of DC-driven activation of naive Th cells draws heavily on events that occur after the stimulation of resting DCs with strong ligands of the innate Toll-like receptors (TLRs), such as lipopolysaccharide, CpG, and others (8). Binding of these molecules to their receptors initiates signaling cascades, primarily through the adaptor MyD88, resulting in stable presentation of major histocompatibility complex II–peptide complexes to T cells (signal 1), and up-regulation of the co-stimulatory molecules CD40, CD80, and CD86 (signal 2). In the generation of a Th1 response, DCs subsequently release interleukin (IL) 12, which can be considered signal 3 (a qualitative signal that directs T cell polarization) (9). Similarly, Th17 may be promoted by DC-derived IL-1, IL-6, or IL-23 (3). For Th2 induction, we know that DCs must likewise express major histocompatibility complex II (10), CD40 (11), CD80, and CD86 (12). However, the Th2-specific drivers, whether DC receptor/ligand pairs and/or a signal 3 counterpart for Th2 cells, have not been identified. In terms of cytokines, IL-4 and IL-10 are both attractive candidates for a Th2-driving signal 3 from DCs, but both IL-4– (13, 14) and IL-10–deficient (15) DCs can still drive Th2 responses. Indeed, DC-produced IL-10 may be more important for the generation of regulatory environments (16) and/or in delaying DC apoptosis in the face of overt stimulation (17) than in directing Th2 development.

Our ignorance of Th2-associated DC signals has led to the view that the mere absence of IL-12 leads, by default, to a Th2 outcome. Although this can occur when T cell receptor–transgenic T cells are stimulated in vitro in the absence of IL-12, this explanation is difficult to apply to more complex in vivo events, as discussed below. Furthermore, in settings where Th2 responses are critical for pathogen clearance or prevention of excess immunopathology, reliance on a default process seems unlikely. In this context, the recent implication of the co-stimulatory tumor necrosis factor superfamily member OX-40L (9, 18, 19) and the Notch ligands jagged1 and jagged2 (20) in the generation of Th2 responses carries

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both mechanistic and polemical significance. Further unraveling of the relative importance of these molecules, and others that will undoubtedly be revealed in due course, is eagerly awaited.

Th2 induction in the absence of overt DC activation?

The range of candidate molecules that DCs must express to efficiently provoke Th2 responses is increasing. However, an intriguing hallmark of DC activation by Th2-type antigens, such as *Schistosoma mansoni* soluble egg antigen (SEA) (21), excretory/secretory material from *Nippostrongylus brasiliensis* (NES) (18), or *Acanthocheilonema viteae* (12), is that the DCs fail to display the conventional suite of stimulation events, such as cytokine production and surface activation marker expression. This muted phenotype is reminiscent of some descriptions of tolerogenic DCs (22), yet these cells are still potently immunogenic and are capable of polarizing Th2 responses both in vitro and in vivo (10, 12, 14, 18, 23, 24). These observations appear to support the idea that Th2 development occurs by default when DCs are activated above their tolerogenic resting state in the absence of TLR ligands. (Fig. 1 A). However, NES was found to induce a Th2 response even when coadministered with potent TLR stimuli in complete Freund's adjuvant (25). When DCs were coexposed to SEA and bacterial antigen, they continued to induce an SEA-specific Th2 response (26). Hence, a Th2 outcome can occur even in the presence of TLR-dependent signals that are capable of driving complete DC maturation and normally induce a Th1 response.

It seems likely that DC activation has more dimensions than we currently appreciate, and the very plasticity of DC function may require a spectrum of distinct activation states to induce each of the different T cell outcomes (8). What is clear at this stage is that the activation phenotype of DCs, as currently measured after stimulation, does not always faithfully predict their ability to influence T cell polarization. Absence of overt DC activation can drive a Th2 response or tolerance induction, and production of IL-12 by DCs does not always guarantee a Th1 response.

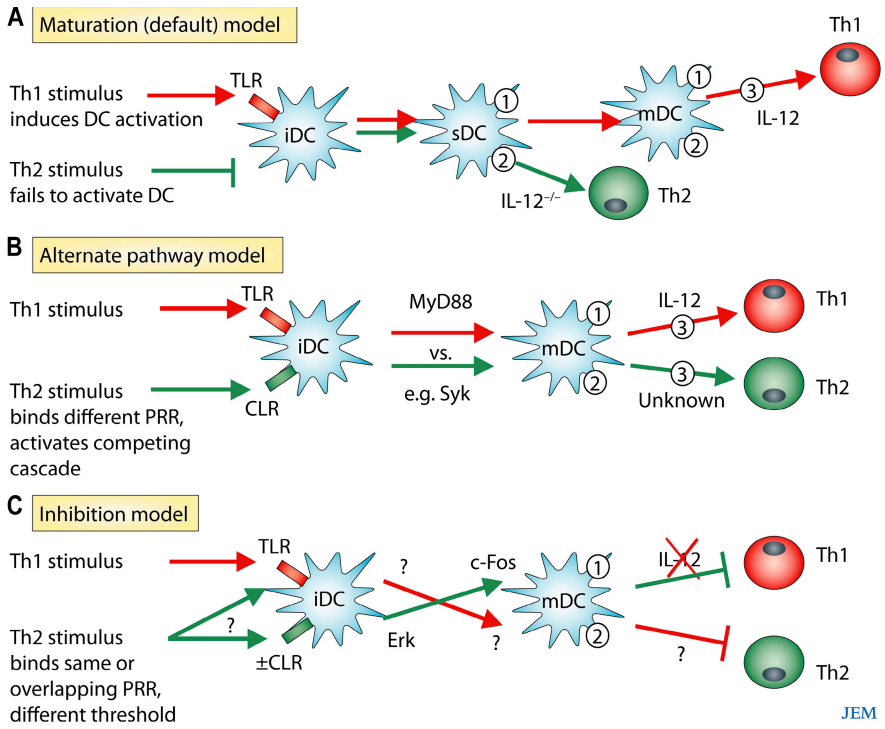

Figure 1. Alternative models for selective Th1/Th2 induction by DCs. (A) The maturation model, which posits that Th1 stimuli drive immature DCs (iDC) to develop into completely mature DCs (mDC) able to induce Th1 via signal 3 (e.g., IL-12) provision to T cells. In contrast, most Th2 stimuli elicit little or no activation, generating semimature DCs (sDC), which fail to provide signal 3. In the absence of complete DC maturation, responses default to the Th2 mode. Because EDN activates DCs (and their secretion of IL-12) while promoting Th2 induction, it does not fit into this scheme. (B) The alternate pathway model, in which Th1 and Th2 stimuli are linked to distinct sets of pattern recognition receptors (PRR), such as TLRs and CLRs. For example, strong signaling through TLRs initiates intracellular cascades, principally involving MyD88, which up-regulate proinflammatory cytokine production, including that of IL-12. In contrast, ligation with a CLR-binding, Th2-inducing stimulus can activate Syk in a pathway that favors IL-10 rather than IL-12, although no consequent signal 3 has been identified (reference 31). The outcome of exposure to complex antigens may depend on the relative strength of signal in two or more competing receptor-dependent pathways. (C) The inhibition model, in which signaling pathways may intersect and inhibit one another. For example, Th2 stimuli that up-regulate ERK phosphorylation and stabilize c-Fos effect an intracellular block on IL-12 production (reference 23). In a complementary fashion, strong TLR4 ligation can negate the ability of SEA to induce Th2 responses, though in this instance the signaling mechanism has yet to be defined (reference 32). The default model is unlikely to hold true in most in vivo Th2 settings, whereas a combination of the alternate pathway and inhibition models is perfectly plausible.

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As Yang et al. now show, EDN provides another example of this separation between the DC activation profile and the kind of Th response with which it is aligned in that it appears to activate DCs similarly to many Th1 antigens and, yet, has Th2-inducing adjuvant properties (6). Human monocyte-derived DCs exposed to recombinant EDN in vitro up-regulated surface activation markers, secreted cytokine, and displayed an altered migration capacity and an increased ability to provoke allogeneic T cell proliferation, a profile typical of conventionally activated DCs. Nevertheless, injection of mice with EDN, or transfer of ovalbumin/EDN-pulsed DCs, generated Th2 rather than Th1 immunity, suggesting that a muted activation phenotype will not always be a prerequisite for Th2 induction by DCs (6).

How are Th2 antigens recognized by DCs?

So far we have very little knowledge of which pathogen-derived molecules bind to which receptors on DCs to confer Th2-inductive capacity. TLRs and MyD88 have been implicated in this process: ligation of TLR2 can induce a Th2 response via extracellular signal-regulated kinase phosphorylation and stabilization of the transcription factor c-Fos (24, 27), schistosome sugars can act via TLR4 to condition Th2-driving DCs (28), and schistosome lipids bind TLR2 to induce IL-10–producing Tr1 cells (23). The triggering of TLR2/MyD88 by EDN shown by Yang et al. (6) is therefore consistent with these other reports of Th2-associated DC stimuli. But conclusive evidence that TLRs or MyD88 have a fundamental role in directing DCs to induce Th2 responses is lacking. And because DC-driven Th2 induction can occur in an MyD88-independent fashion (14), it may be that Th2 responsiveness is not as dependent on the MyD88 pathway as is Th1.

Recently, C-type lectin receptors (CLRs) have drawn attention both as markers of DC subsets and as initiators of key signaling events within the DCs (29). Information about the range of CLRs bound by Th2-skewing pathogens is currently limited. But schistosome components have been shown to interact with a variety of CLRs expressed by DCs, including DC-SIGN, macrophage-galactose type lectin, and the mannose receptor, and this may affect internalization of the antigen and the shifting capacity of the DCs to polarize T cells (30).

Can CLR signaling influence Th cell subset instruction? The β-glucan receptor dectin-1 (CD37) may act in this capacity. Dectin-1 signals via Card9 (31) and Src/Syk (32), and Syk$^{-/-}$ DCs mediate a more IL-12–dominated response. Thus, a plausible scenario is that MyD88-dependent, pro-Th1 signals compete with pro-Th2 signals mediated through molecules such as Syk (Fig. 1 B). Interestingly, the dectin-1 and TLR2 pathways synergize (32), indicating that competition or positive reinforcement can occur in different settings.

Th1 versus Th2: competition or inhibition?

If Th1 and Th2 ligands initiate distinct, but intersecting, signal cascades, is their interplay simply competitive or is there cross-inhibition at the molecular level (Fig. 1 C)? Negative signaling might well account for the ability of Th2 ligands to suppress DC-driven induction of Th1 responses (14, 27). The most prominent example of interference with Th1 induction by Th2-driving molecules is the blocking of IL-12 production (either or both p40 and p70) in DCs pretreated with NES or SEA before LPS challenge (14, 18, 26). Th1-inducing agents can, in turn, block Th2 outcomes. In this

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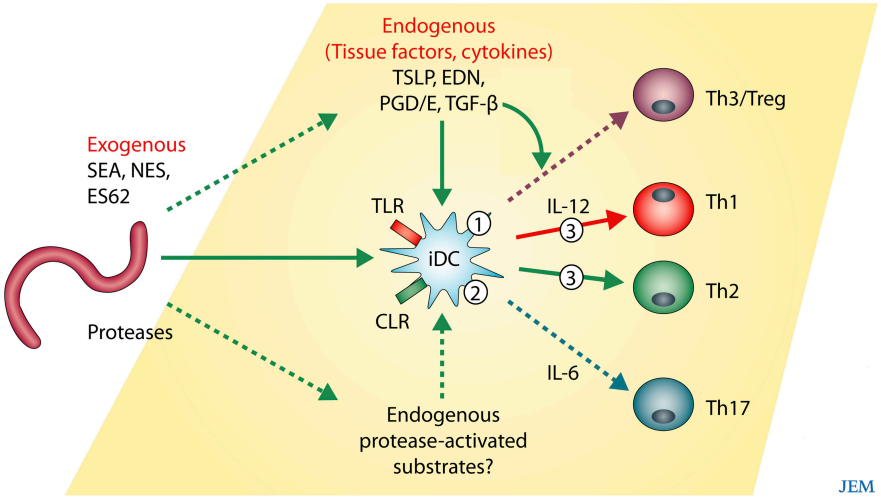

Figure 2. Exogenous and endogenous Th2–inducing stimuli acting through DCs. Th2 stimuli include both exogenous and endogenous ligands. Examples from parasites include SEA (reference 9), NES (reference 17), and *Acanthocheilonema viteae* excretory secretory 62-kD antigen (ES62; reference 11), which directly drive Th2 induction through DCs. Proteases released from parasites or contained within allergenic material may activate endogenous substrates to initiate the Th2 pathway. Endogenous tissue factors that promote Th2 include TSLP and EDN, as well as prostaglandins D and E, which may also be produced or induced by parasitic helminths (green dashed arrow). It is not known if endogenous tissue factors may also act directly on developing T cells to influence subset choice, but two key cytokines (transforming growth factor β and IL-6) are included for their role in T reg and Th17 induction.

case, Th2 development can be directly countermanded by TLR ligation, which blocks IL-4 production and IL-2–responsive STAT-5 phosphorylation in DCs (33). A requirement for negative signaling to block Th2 responses is inconsistent with a linear maturational model of Th2 induction (Fig. 1 A) unless it is postulated that Th2 induction occurs subsequent to Th1 (34).

An attraction of both competition and inhibition models is that they would be highly quantitative, permitting the balance of responsiveness to be calibrated according to the input of competing signals. This type of model can also accommodate "flip-flop" mechanisms of activation in which ratios of key antagonists can switch the Th outcome in response to small increments in stimuli. These models better accommodate the longitudinal dynamics of the Th response to infections, which can switch over time, and also permit endogenous ligand signaling to fine tune the quality of response. In this context, it would be interesting to test if mediators such as EDN can still drive a Th2 response in competition with an active Th1-inducing stimulus, and if the activity of the ligand on DCs differs depending on whether it is present at low, constitutive levels or at higher, infection-induced levels.

Complexity of the environment in vivo

A great deal of the information we now have about how DCs generate Th2 responses (Fig. 2) has been gleaned from reductionist systems that do not incorporate the spectacular complexity of the in vivo immune response. DCs do not act in isolation when communicating with T cells. On the contrary, they are highly gregarious and likely interact with a whole network of cell types before, during, and after the defining Th cell–polarizing encounter. Contacts between DCs and epithelial cells, mast cells, natural killer cells, and others are unlikely to be one-sided conversations, and the end result is likely to be both an altered DC activation state and a modified immune environment. The release of antimicrobial proteins and peptides in response to infection, injury, or cytokines adds yet another layer of complexity to this scenario.

This encapsulates a general principle: the DC gauges its environment at many levels. Alarmins, tissue factors such as TSLP (5), and the cytokine and chemokine cocktail surrounding the DC are all part of the environmental equation on which the Th1/Th2 switch-point depends (35). Indeed, it is entirely possible that the elusive signal 3 for Th2 cells is provided not by DCs but by other cell types in the tissue setting. We can only speculate which members of the up-and-coming range of Th2-associated mediators, such as YM-1, resistin-like molecules α and β (36), IL-21 (37), and IL-25 (38), may also be involved in such a process.

An example of how this complexity translates into functional properties of DCs in vivo is provided by studies of human colonic DCs, which are skewed toward Th2 induction (38). A similar state can be induced in monocyte-derived DCs either by incubation in epithelial cell supernatants or by addition of TSLP (39). More broadly, the frequency of $CD103^+$ DCs, which are associated with the induction of T reg cells, is significantly higher in mucosal tissues than in the spleen (40). Hence, the local environment is coordinated with local DC populations to induce the most appropriate mode of response.

EDN is a mediator that can multitask. But what mechanisms determine which hat EDN will wear at any one time? And how representative is the Th2 nature of EDN or of other antimicrobial proteins or peptides, alarmin or otherwise? Although eosinophils can produce EDN, several additional potential sources exist, including other granulocytes, macrophages, and epithelial cells. It will be fascinating to learn which cell type provides the predominant source of EDN after immune challenge, and whether different cells take on this role depending on the nature of the challenge. It will be equally interesting to figure out the extent of interplay between EDN and other tissue factors during immune activation, the net effect of this interplay on DC activation and function, and whether this might differ in acute versus chronic settings. In particular, when considering chronic exposure and Th2 maintenance, will DCs retain their preeminence or will other antigen-presenting cells (such as B cells) supercede them?

Conclusion

We can now conclude that both Th1 and Th2 stimulations are active processes, albeit using different suites of signals. Perhaps the true default pathway is homeostatic maintenance of tolerance by resting DCs unruffled by tissue factors, alarmins, or foreign molecules. The actual mechanism of Th2 induction via DCs, whether in response to exogenous (e.g., helminth) or endogenous (e.g., EDN) ligands, is still poorly understood. At this point, we cannot be sure that there is a single mechanism or whether a combination of passive (default), active (induction), and competitive pathways are at play. EDN is a new and important character in the roll call of Th2-promoting factors, illustrating the intimacy and complexity of communication between host tissues and the decision-making machinery of the immune system.

The laboratories of A.S. MacDonald and R. Maizels are supported by the Wellcome Trust and the Medical Research Council.

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