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Invited Review

Dendritic cell activation and function in response to *Schistosoma mansoni*

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Abstract

Dendritic cells (DC) are uniquely specialised for both antigen acquisition and presentation, linking innate and adaptive immunity. Their central role in the activation of naïve T cells gives DC a strategic position in the control of immune responses. While the mechanisms by which viral, bacterial or protozoal pathogens interact with and activate DC are increasingly understood, much less is known about how these cells react to more complex organisms such as schistosomes. Recent studies have examined the impact on DC of antigens from different life cycle stages of *Schistosoma mansoni* and have revealed a DC phenotype quite distinct to that of conventional activation. Schistosome antigens elicit little of the cytokine secretion and costimulation that are abundantly triggered in DC by unicellular, proinflammatory pathogens and indeed may even actively inhibit such events. The DC response is not a null one, however, since *S. mansoni* -exposed DC still act as potent antigen presenting cells capable of generating a powerful Th2 immune response. Understanding the interaction between schistosomes and DC is therefore not only addressing fundamental questions of DC biology and immunity to multicellular parasites but also opens the way to therapeutic manipulation of the immune system.

Keywords: Schistosomes; Dendritic cells; Th1/Th2; Cytokines; Costimulation

1. Introduction

Schistosome infection presents a complex challenge to the immune system. The parasite is a multicellular organism which exists in discrete life stages and inhabits multiple locations within the host. The outcome of the immune response determines the balance between protective immunity and immunopathology, the difference between health and morbidity (Pearce and MacDonald, 2002). Dendritic cells (DC) are central players in the control of developing immune responses, specialised in both the initiation and polarisation of adaptive immunity (Banchereau et al., 2000; Moser and Murphy, 2000). Here, we present an overview of current understanding of the interactions between DC and schistosomes, emphasising the distinctive DC phenotypes elicited by schistosome components and the potent ability of these cells to drive T helper cell (Th) type 2 immunity in vivo.

'Immature' DC are often described as the sentry guards of the immune system, stationed throughout the peripheral tissues, continuously sampling their environment through phagocytosis, endocytosis and macropinocytosis (Sallusto et al., 1995; Winzler et al., 1997). They filter soluble antigens from extracellular fluid at such a rate that they internalise the equivalent of their own volume within 2 h (Sallusto et al., 1995).

Recent years have seen the description of a plethora of defined pattern recognition receptors (PRRs) expressed by DC that can recognise and bind with pathogen-associated molecular patterns (PAMPs) displayed by infectious organisms such as bacteria and viruses (Janeway, 1989). If 'danger' signals are encountered by DC in the form of PAMPs, inflammatory cytokines or signals from activated T cells, a process of classical 'maturation' is triggered and they transform from dedicated antigen (Ag) collectors into specialised Ag presenting cells (APC) (Matzinger, 2002). DC migration towards naïve T cells in the draining lymph node (LN) is accompanied by a significant up-regulation and stabilisation of surface major histocompatability molecules (MHC) (Cella et al., 1997; Pierre et al., 1997), increased expression of key

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costimulatory molecules such as CD80 and CD86, intracellular adhesion molecule-1 (ICAM-1) and CD40 and an enhanced readiness to secrete T cell stimulatory cytokines such as IL-12 (Kang et al., 1996; Reis e Sousa et al., 1997) and IL-2 (Granucci et al., 2001). The result is a potent APC, equipped to interact with and activate naïve T cells (Bhardwaj et al., 1993; Sallusto et al., 1995).

The best studied examples of the PRRs are provided by the *Toll*-like receptors (TLRs), a family of proteins largely responsible for triggering conventional maturation in dendritic cells exposed to proinflammatory, Th1-driving pathogens (Akira and Takeda, 2004; Beutler, 2004). Whether a set of equivalent but Th2-polarising receptors will be uncovered or whether the existing TLRs are sufficient to orchestrate both types of response is still a matter of debate. In addition to TLRs, recognition of Ag by DC is also mediated by C-type lectins such as DC-specific intracellular adhesion molecule three grabbing nonintegrin (DC-SIGN or CD209), DEC-205 (CD205) and Dectin-1 (Figdor et al., 2002; Geijtenbeek et al., 2003; van Kooyk and Geijtenbeek, 2003; Rogers et al., 2005). Interestingly, there is evidence that signaling via C-type lectins may in some cases inhibit DC maturation, a feature that appears to have been exploited by certain pathogens (Geijtenbeek et al., 2003).

In the past few years, it has become clear that the paradigm of the conventionally mature, immunogenic DC is not always a valid one. Different DC phenotypes can direct immune responses as diverse as immunity and tolerance (Lutz and Schuler, 2002). Several main subpopulations of DC exist, identified on the basis of expression of particular surface markers and isolated from specific tissues; 'lymphoid' (CD11c+/CD8α+), 'myeloid' (CD11c+/CD8α−) and 'plasmacytoid' (CD11c+/B220+) DC. Initial experiments suggested that different lineages possessed distinct functions that preferentially induced either Th1 or Th2 responses (often termed 'DC1' and 'DC2') (Maldonado-Lopez et al., 1999; Pulendran et al., 1999; Rissoan et al., 1999; Shortman and Liu, 2002). More recent work, focussing on the DC response to pathogen-derived rather than model antigens, has revealed that, while DC subsets may differ in the limits of their possible function, all are capable of assessing the nature and context of an Ag and tailoring the immune response appropriately (Kalinski et al., 1999; Kapsenberg, 2003; Manickasingham et al., 2003). Thus, the restrictive idea of lineage determination has been largely replaced with a model of functional plasticity, in which the complex mélange of molecular information presented by pathogens is recognised and translated into polarised T cell activity by local DC. This concept of DC plasticity makes sense given that the mammalian immune system has arguably developed as a consequence of evolutionary interactions with pathogens.

Kalinski and colleagues coined the term 'signal 3' to describe the polarising instructions delivered to naïve T cells by DC alongside T cell receptor (TCR) engagement ('signal 1') and CD80/86:CD28 interaction ('signal 2') (Kalinski et al., 1999). Their model noted the potent ability of DC-derived IL-12 to skew towards interferon γ (IFNγ) production in responding T cells, an observation which Reis e Sousa expanded in his description of an IL-12/IL-10 axis of DC maturation: pathogen products elicit high levels of either IL-12 or IL-10 from DC and only those that generate IL-12 drive strong Th1 responses (Edwards and Reis e Sousa, 2002). Thus, the cytokines released by DC and those consequently triggered downstream appear to reflect the specific activation of these cells by distinct pathogens.

To date, our appreciation of these processes of DC activation and function remains heavily biased towards data collected in experiments focussing on model antigens or components of pathogens such as bacteria, viruses or protozoa that typically induce Th1 responses (Reis e Sousa et al., 1999). The DC response to multicellular organisms is much less understood. Of the three main human-infective species of schistosome (*Schistosoma mansoni*, *Schistosoma hematobium* and *Schistosoma japonicum*), the immune response to and immunopathology caused by *S. mansoni* has been most extensively dissected. This response is strongly Th2 in nature and detailed analysis has revealed that the major Th2 stimulating Ag are soluble and released from the egg stage (Grzych et al., 1991; Pearce et al., 1991). It is clear that the Th2 response provides protection against potentially life-threatening aspects of ongoing infection, as well as against superinfection (Brunet et al., 1998, 1999; Fallon et al., 2000; Hoffmann et al., 2000). At the same time, the Th2 response is intimately involved in the development of much of the pathology that accompanies infection, including tissue fibrosis (Pearce and MacDonald, 2002). Despite its importance, the mechanisms that control the development of the Th2 response, how it is regulated and how it serves its protective role are still largely unknown (Pearce and MacDonald, 2002).

2. The dendritic cell: parasite interface

Several years ago, we set out to address the fundamental immunological question of how DC respond to Th2-inducing pathogens and, mechanistically, how they subsequently initiate and direct the Th2 response, focussing on the murine response to *S. mansoni*.

The interaction between parasite and DC begins with recognition of specific components of the antigenic mix encountered by the host. All life cycle stages of *S. mansoni* produce a complex range of molecules—proteins, carbohydrates and lipids—some of which have been extensively characterised and any of which could be considered potential candidates for innate recognition during infection. The fact that many years of searching has failed to identify a successful single vaccine candidate from amongst these molecules suggests that recognition of multiple components simultaneously provides the appropriate molecular 'key' for full immune recognition of schistosomes (Pearce, 2003).

3. Dendritic cell activation by *S. mansoni*

Of all the life cycle stages of *S. mansoni*, we currently know the most about the ability of soluble egg Ag (SEA) to influence

DC activation. SEA is a complex mix of diverse components that is crudely analogous to the metabolic secretions of live eggs. Notably, each of SEA, live or dead *S. mansoni* eggs provoke a striking Th2 response when injected directly into naïve recipient mice, without the need for additional adjuvant. Indeed SEA, like some other helminth products or extracts (Holland et al., 2000), could itself be described as an adjuvant, as it is able to promote Th2 development to co-administered model antigens (Okano et al., 1999, 2001). Further, constituents of SEA have been identified that interact with and activate a variety of innate cells, including mast cells and eosinophils (Sabin et al., 1996; Schramm et al., 2003). The remarkable Th2 immunogenicity of the egg stage of the parasite, coupled with the well-documented role of the egg-driven response in immunopathology, are the reasons why SEA has been, and remains, the focus of ongoing studies (Pearce and MacDonald, 2002).

3.1. DC phenotypic activation and cytokine production in response to S. mansoni

The first reports detailing the response of DC to *S. mansoni* provided surprising results. Murine bone-marrow derived DC (BM-DC) that were exposed to SEA failed to respond in a conventional way. In marked contrast to classical maturation stimuli, SEA provoked only minor up-regulation of MHC Class II on DC, and no significant up-regulation of other hallmarks of maturation such as CD80, CD86, CD54, CD40 or OX-40L (MacDonald et al., 2001). Additionally, SEA-pulsed DC did not produce, either at the protein or the mRNA level, any measurable IL-12p40, IL-12p70, tumour necrosis factor (TNF) or IL-6. Perhaps most notably, SEA did not induce IL-10 or IL-4 production by DC. Similar results were observed for DC exposed to dead *S. mansoni* eggs. Subsequently, this muted in vitro activation of murine DC by SEA has been repeated in several other labs, using either BM-DC (Zaccone et al., 2003) or splenic DC (Jankovic et al., 2004), and comprehensively supported by use of microarray analyses (Kane et al., 2004). This approach revealed that of the 12,000 or so well-characterised mouse genes present in the array used, less than 30 were significantly altered by exposure of DC to SEA, none of which appeared to be obvious candidates for induction of Th2 responses (Kane et al., 2004). In contrast to the very limited effect of SEA, more than 550 genes on the same array showed altered expression in response to conventional maturation stimulus lipopolysaccharide (LPS).

Further emphasizing their unconventional activation status, SEA-pulsed BM-DC do not lose the ability to endocytose fluoresceine isothiocyanate (FITC)-Dextran (unpublished observations). This is surprising, since loss of endocytic capacity is a feature of conventional DC maturation. SEA also appears to be unusually localised and perhaps alternatively processed after uptake by DC, being sequestered to $Lamp2^{-}$ or $Lamp2^{dull}$, $Transferrin^{-}$ compartments within BM-DC, as opposed to the $Lamp2^{+}$ $Transferrin^{+}$ compartments entered by a heat killed Gram+ bacteria control (*Propionebacterium acnes*) (Cervi et al., 2004).

Curiously, although SEA and dead *S. mansoni* eggs fail to conventionally mature murine DC (MacDonald et al., 2001), live eggs appear to behave differently. In a recent study, live *S. mansoni* eggs derived from infected hamsters elicited the transcription of a range of genes in murine DC that one might at first glance associate with Th1, rather than Th2 response induction (including IL-12p40, TNF and type I IFN) (Trottein et al., 2004). A subsequent intriguing report from the same group indicated that live egg-derived double stranded RNA (dsRNA), binding via TLR3, may be the signal that drives this activation phenotype (Aksoy et al., 2005). Neither of these studies addressed the ability of the DC to drive an appropriate immune response to *S. mansoni*.

The effect of SEA on human DC appears to be subtly different to that seen with murine cells. The available data indicate that human monocyte-derived DC (mDC) exposed to SEA in vitro display a level of phenotypic activation, although less than that induced by conventional maturation stimuli such as LPS (de Jong et al., 2002; Agrawal et al., 2003). However, in keeping with what is seen with murine DC, human DC produce little detectable IL-12p70, TNF or IL-10 in response to SEA (de Jong et al., 2002; van der Kleij et al., 2002; Agrawal et al., 2003). An important, though technically challenging, next step will be to assess the activation status of DC isolated directly from humans actively infected with *S. mansoni*. This will allow us to guage the physiological relevance of the data gained from studies that have exposed human DC (cultured from PBMC) to SEA in vitro.

In terms of the response of DC to *S. mansoni* life cycle stages other than the eggs, it appears that soluble schistosomulum Ag (SSA) and soluble adult worm Ag (SWA) also fail to conventionally activate murine DC (Zaccone et al., 2003; Trottein et al., 2004). However, BM-DC exposed to the material released by infectious cercariae during the first 3 h post-transformation (termed 0–3 h released preparation, 0–3 hRP), only partially resembled the restricted activation state of DC stimulated with SEA, dead eggs or SSA referred to above. This 0–3 hRP induced an intermediate activation state characterised by limited up-regulation of MHCII, CD40 and CD86 expression and IL-6 and IL-12p40 production (Jenkins and Mountford, 2005). It remains to be seen how Ag derived from *S. mansoni* lung stage larvae affect murine or human DC activation.

3.2. DC signaling in response to S. mansoni

Relatively little is known about signaling events in DC in response to schistosome Ag. Several reports have indicated that exposure of DC to SEA or components of SEA is associated with mitogen-activated protein kinase (MAPK) phosphorylation and requires expression of NF-κB1 (Agrawal et al., 2003; Thomas et al., 2003; Kane et al., 2004; Artis et al., 2005). Undoubtedly, there remains much to be learned about signaling events in DC after their exposure to schistosome Ag.

3.3. DC activation during S. mansoni infection

Attempting to define DC activation during ongoing infection with *S. mansoni* obviously provides a significant

challenge, presenting a much less controlled experimental system than in vitro models. Despite this complexity, rodent models of *S. mansoni* infection have already started to yield interesting information about DC activation by the parasite in vivo.

In the early stages of schistsosome infection, larvae in the skin site of exposure induce an inflammatory reaction and cellular influx that includes DC (Riengrojpitak et al., 1998; Hogg et al., 2003a). There is also evidence for the activation and maturation of DC in the skin following cercarial penetration, as determined by up-regulation of MHC II and CD86 expression, albeit coinciding with delayed migration (Riengrojpitak et al., 1998; Angeli et al., 2001; Hogg et al., 2003a,b). Intriguingly, experiments using *S. mansoni*-infected mice indicated that cercarial-derived prostaglandins (PGD_2) appear to interfere with migration of Langerhans cells from the site of larval penetration to the skin-draining lymph nodes (Angeli et al., 2001). Related to this, earlier experiments in which guinea pigs were infected with *S. mansoni* showed enhanced Langerhans cell recruitment following percutaneous exposure to UV-attenuated compared with normal *S. mansoni* cercariae (Sato and Kamiya, 1998). Together, these data raise the interesting possibility that attenuated cercariae may themselves exhibit impaired PGE_2 production or secretion as well as being less effective at provoking PGE_2 from host skin cells (Ramaswamy et al., 2000).

Further evidence for the generally muted activation of CD8α− BM-DC by *S. mansoni* in vitro is provided by the fact that both CD8α+ and CD8α− subsets of DC isolated from the spleen or mesenteric lymph nodes over the course of murine infection with *S. mansoni* (from weeks 4 to 15) display only minor up-regulation of expression of conventional activation markers (Straw et al., 2003). Mechanistically, it appears that phenotypic activation of DC by *S. mansoni* in vivo is promoted by CD40:CD154 interaction and inhibited by IL-10. DC isolated from *S. mansoni* infected $CD154^{-/-}$ mice fail to display evidence of even low-level activation (Straw et al., 2003), whereas DC isolated from infected IL-$10^{-/-}$ mice display a hyperactivated phenotype (McKee and Pearce, 2004). It is currently unclear how other types of DC (including liver, gut and plasmacytoid DC) respond to *S. mansoni* exposure, either in vivo during infection or in vitro.

4. T cell activation and polarisation by dendritic cells responding to *S. mansoni*

Around the time that data were emerging describing the subdued activation of DC by schistosome Ag, a new facet of DC biology was also being described—their ability in certain settings to be tolerogenic rather than immunogenic (Lutz and Schuler, 2002; Steinman et al., 2003). This was noted when DC were exposed to Ag that did not provide activatory 'danger' signals such as apoptotic cells or commensal bacteria. Notably, such DC failed to show overt signs of conventional maturation, which was hypothesised to be responsible for anergy in responding T cells (Lutz and Schuler, 2002). The subdued activation phenotype of SEA-exposed DC, as well as being strikingly similar to the description of tolerogenic DC, resembled several pathogen:host systems where the pathogen in question appeared to inhibit or interfere with DC activation and function (Grosjean et al., 1997; Salio et al., 1999; Urban et al., 1999). In this context, the absence of conventional maturation of DC exposed to Ag from the cercarial, schistosomulum, or egg stages of the life cycle of *S. mansoni* (0–3 hRP, SSA, or SEA) suggested that *S. mansoni* renders DC unable to activate naïve T cells.

In fact, SEA-pulsed DC proved to be extremely potent activators of naïve T cells, inducing a definitive SEA-specific Th2 response after transfer into naïve recipient mice (MacDonald et al., 2001; Faveeuw et al., 2002) or co-culture with ova-specific T cell receptor-transgenic T cells (Jankovic et al., 2004). Murine DC exposed to dead *S. mansoni* eggs also drive a marked Th2 response after transfer in vivo into naïve recipient mice (unpublished observations). Akin to what is seen with SEA or dead eggs, DC activated with cercarial 0–3 hRP acquire the capacity to drive Th2 polarisation associated with abundant IL-4, IL-5, and IL-10 production both in vitro and in vivo (Jenkins and Mountford, 2005). This questions the generally accepted idea that the early larval stages of the parasite are poorly immunogenic and more Th1 stimulatory than Th2 in character. However, further complicating our understanding of these early stages of interaction of schistosomes with the innate immune system and perhaps more in keeping with expectation, soluble schistosomulum Ag appears to confer on DC only a weak ability to drive a mixed Th1/Th2 response (Faveeuw et al., 2002). The character of the immune response induced by DC exposed to Ag derived from *S. mansoni* lung stage larvae or adult worms has yet to be determined. Table 1 summarises the current literature on DC activation and function in response to different life cycle stages of *S. mansoni*.

The fact that Ag-loaded DC were alone sufficient to drive Th2 polarisation was somewhat surprising, but illustrates the potent ability of DC as APC. This suggests that input from other innate immune cells recognising and responding to components of the parasite is not a fundamental requirement for Th2 induction. However, it is likely that a network of additional cell types contributes to the emergent T cell polarisation phenotype during both induction and amplification of the developing T cell response by DC in vivo. For example, recent reports suggest that innate cells such as natural killer (NK) cells can be directly activated by DC transferred in vivo (Martin-Fontecha et al., 2004). Exactly how this communication occurs in the absence of free Ag is currently unknown, but DC secretion of cytokines or transfer of intact Ag may both be involved (Wykes et al., 1998). Perhaps related to this, a role for CD1d-restricted NKT cells has been suggested during SEA-driven Th2 response induction in vivo (Faveeuw et al., 2002; Zaccone et al., 2003).

4.1. DC cytokine production and Th2 induction in response to S. mansoni

Since the cytokines released by activated DC profoundly influence the polarisation of a developing immune response,

Table 1
Dendritic cell activation and function in response to different life cycle stages of *Schistosoma mansoni*

Stimulus	Phenotype		Cytokine production					T-cell polarisation	Refs.
	MHCII	CD40/80/86	IL-12p40 IL-6 TNF	IL-12p70	IL-10	IFNα	IL-2		
None	lo	lo	lo	–	–	–	–	–	
LPS	hi	hi	hi	hi	hi	hi	hi	Th1	
SEA	int	lo	lo	–	–	ND	–[a]	Th2	1-4
Dead eggs	int	lo	lo	–	–	ND	ND	Th2[a]	1
Live eggs	ND	ND	hi	–	ND	hi	hi	ND	5
0–3 hRP	int	int	int	–	–	ND	ND	Th2	6
SSA	ND	ND	lo	–	–	–	–	Th1/Th2	2,5
SWA	int	lo	lo	–	–	ND	ND	ND	3

SEA, soluble egg Ag. SWA, soluble adult worm Ag. 0–3 hRP, post-transformation cercarial secretions. SSA, soluble schistosomulum Ag. LPS, lipopolysaccharide. N.D., not done. References: 1; (MacDonald et al., 2001), 2; (Faveeuw et al., 2002), 3; (Zaccone et al., 2003), 4; (Jankovic et al., 2004), 5; (Trottein et al., 2004), 6; (Jenkins and Mountford, 2005).
[a] Unpublished observations. lo, int, hi, low, intermediate or high level expression or production. ND, not done. SWA, soluble adult worm Ag.

an initial assumption was that schistosomes and other pathogens that induce Th2 responses might do so by directly stimulating IL-4 production by DC. Although there are isolated reports in the literature suggesting that DC may possess the ability to produce IL-4 (d'Ostiani et al., 2000), we and others have consistently failed to find any evidence for IL-4 production, either at the protein or mRNA level, by DC in response to SEA or any other stimulus that we have tested (MacDonald et al., 2001). Significantly, IL-4-deficient murine DC are just as able to drive SEA-specific Th2 responses as their wild type equivalents, both in vivo and in vitro (MacDonald and Pearce, 2002a; Jankovic et al., 2004), clearly ruling out a requirement for BM-DC or splenic DC-derived IL-4 in Th2 induction by SEA.

Experiments examining DC:pathogen interactions raised the possibility that it may be IL-10 rather than IL-4 which opposes IL-12 in the decision between Th1 and Th2 fate (Manickasingham et al., 2003). The effects of IL-10 have been associated with both Th2 promotion (Maldonado-Lopez et al., 2001; Dillon et al., 2004; Klechevsky et al., 2005) and T cell tolerance (Takayama et al., 1999; McGuirk et al., 2002) and DC-derived IL-10 can limit Th1 expansion both through its autocrine inhibition of IL-12 release (Corinti et al., 2001) and by its ability to stimulate IL-10 release from T cells later in the immune response (McGuirk et al., 2002). IL-10 is not an absolute requirement for Th2 induction to SEA in vivo, however. IL-10 production by DC exposed to SEA cannot be measured by either protein detection (MacDonald et al., 2001) or gene expression (Kane et al., 2004). Most notably, SEA-pulsed IL-10-deficient DC are equally as potent as wild type DC at inducing a Th2 response and SEA-pulsed DC can elicit a Th2 response in IL-10 deficient animals that is reduced but not absent (Perona-Wright and MacDonald, unpublished). Interestingly, this reduction in the Th2 response correlates with the emergence of SEA-specific IFNγ, perhaps suggesting that the role of IL-10 in Th2 promotion is to negate the counter-regulatory influence of Th1 cytokines, rather than to directly promote Th2 development.

4.2. *Costimulation and Th2 induction in response to* S. mansoni

Surprisingly, even though DC exposed to SEA do not up-regulate CD40 (MacDonald et al., 2001), CD40-deficient murine DC fail to stimulate SEA-specific Th2 development (MacDonald et al., 2002b). Further, CD154-deficient mice infected with *S. mansoni* fail to develop a Th2 response (MacDonald et al., 2002c). Although the concept of CD40-mediated 'licensing' of DC function is not new, it has mainly been focused on Th1 amplification through increased IL-12 production (Cella et al., 1996; Reis e Sousa et al., 1997) and DC involvement in CD8 T cell responses (Bennett et al., 1998; Ridge et al., 1998). However, CD40 signaling can result in more than simply amplification of IL-12 production by DC. In particular, it can boost expression of a wide range of costimulatory molecules on DC, including CD80, CD86, CD70, 41BBL and OX40L (Cella et al., 1996; Chen et al., 1999; Diehl et al., 2002; Tesselaar et al., 2003). The reliance

Table 2
Putative pathogen associated molecular patterns from *S. mansoni* and the pattern recognition receptors they may bind

	Life cycle stage[a]				Potential receptor	T-cell response	Refs.
	C	S	A	E			
Glycoproteins containing:							
α3-fucose	+	+	+	++	–	Th2	Faveeuw et al. (2003)
β2-xylose	+	+	+	++	–	Th2	Faveeuw et al. (2003)
Specific examples:							
Lewis^X		+		+	DC-SIGN	ND	van Die et al. (2003)
Lewis^Y	+				DC-SIGN	ND	Meyer et al. (2005)
LNFPIII[1]				+	TLR4/DC-SIGN	Th2	Thomas et al. (2003) and Meyer et al. (2005)
LDNF				+	DC-SIGN	ND	van Die et al. (2003)
Lyso PS			+	+	TLR2[b]	Tr1/Th2[b]	van der Kleij et al. (2002)
dsRNA				+	TLR3	ND	Aksoy et al. (2005)

TLR, *Toll*-like receptor; +, present; ++, present at high level. ND, not done; LNFPIII contains the Lewis^X trisaccharide.
[a] C, cercaria, S, schistosomulum, A, adult, E, egg.
[b] Tr1, but not Th2, induction by Lyso PS is TLR2-dependent.

of SEA-pulsed DC on CD40 expression for Th2-inducing ability suggests a role for molecules downstream of CD40 in this process. Related to this, human mDC expression of OX40L has been shown to be important for SEA-driven Th2 polarisation in vitro (de Jong et al., 2002). Given the wide range of molecules that can be up-regulated on DC following CD40 ligation, it is unlikely that OX40:OX40L will be the only costimulatory partnership involved in Th2 induction by *S. mansoni*. Evidence exists that ICOSL:ICOS and B7:CD28 interactions may be important for Th2 development during *S. mansoni* infection (Hernandez et al., 1999; Rutitzky et al., 2003). Interestingly, culture of DC activated with cercarial 0–3 hRP with agonistic anti-CD40 mAb actually reduced their ability to prime for IL4 and IL-5 production and instead led to IFNγ production (Jenkins and Mountford, 2005). Similarly, in vivo administration of anti-CD40 mAb following *S. mansoni* egg injection induced a switch in the Th response generated in the draining LN, with enhanced IFNγ and reduced IL-4, IL-5 and IL-13 production (Martin et al., 2000). These results may simply be due to the anti-CD40 mAb providing a much weaker signal than the natural ligand CD154 and essentially blocking effective CD40 signaling to the DC. Alternatively, anti-CD40 mAb treatment may actually provide a much stronger signal through CD40 than would normally be encountered in vivo, exceeding the threshold required for Th2 generation and resulting in production of factors favoring Th1 response generation.

4.3. Signaling requirements for Th2 induction by DC in response to S. mansoni

Understanding of the involvement of signaling in the ability of DC to influence T cell activation is currently in its infancy. However, expression of NF-κB1, which appears to be vital for Th2 development in response to injection with schistosome eggs, is also required for regulating activation of the MAPK pathway in DC exposed to SEA and conferring on them Th2 driving ability (Artis et al., 2005).

4.4. Putative PAMPs from S. mansoni *and the PRRs they may bind*

Both lipid and carbohydrate components of *S. mansoni* life cycle stages may play important roles in recognition by, and conditioning of, DC and several reports indicate that DC can bind schistosome components via both TLRs and C-type Lectins (van der Kleij et al., 2002; Thomas et al., 2003; van Die et al., 2003; Aksoy et al., 2005; Meyer et al., 2005) (Table 2). As mentioned above, schistosome egg-derived dsRNA has been reported as a ligand for TLR3 (Aksoy et al., 2005) and TLR4 has been implicated in the ability of glycans from SEA (Lacto-*N*-fucopentaose III) to promote Th2 cell development (Thomas et al., 2003). Human mDC exposed to a lipid component (lysophosphatidylserine—lyso-PS) fractionated from either *S. mansoni* eggs or adult worms were able to polarise allogeneic T cells towards Th2 development in vitro, a process which was shown to be TLR2-independent

(van der Kleij et al., 2002). However, the ability of lyso-PS-exposed DC to induce IL-10-producing T cells (rather than Th2 cells) required TLR2 expression (van der Kleij et al., 2002). While some of these reports implicate TLRs in the induction of Th2 responses by schistosomes, this remains an area of some controversy, particularly since it is clear that the *S. mansoni*-specific Th2 response can develop in the absence of MyD88 (Jankovic et al., 2002; Layland et al., 2005), a key adaptor molecule that is thought to be important for signaling via all TLR, with the possible exception of TLR3 (Kawai et al., 1999; Oshiumi et al., 2003). Additionally, the ability of murine splenic DC to be conditioned by SEA to drive Th2 responses in vitro is MyD88-independent (Jankovic et al., 2004).

The C-type lectin DC-SIGN has been shown to bind the glycan Ag Lewis^x (Galbeta1,4(Fucalpha1,3)GlcNAc) from SEA (van Die et al., 2003), as well as glycolipids from *S. mansoni* cercariae (Meyer et al., 2005). This may be functionally important, since binding of *Mycobacterium tuberculosis* components to DC-SIGN has previously been shown to inhibit the production of IL-12 and promote the production of IL-10, by DC (Geijtenbeek et al., 2003).

5. DC, S. mansoni, and 'default' Th2 reponse development

One proposal has been that Th2 induction by DC occurs via a default pathway that develops in the absence of Th1 driving stimuli, particularly IL-12 (Moser and Murphy, 2000; Eisenbarth et al., 2003). Such a passive situation may occur when DC and T cells are co-cultured in vitro, especially when DC are exposed to model Ag that do not express pathogenic PAMPS. However, since this passive model for Th2 induction was introduced, our understanding of the critical contribution that the type of pathogen encountered makes to plasticity of DC function has increased markedly (Boonstra et al., 2003; Kapsenberg, 2003; Manickasingham et al., 2003), forcing re-evaluation of the relevance of the default concept. Further, the absence of IL-12 in pathogenic settings does not tend to lead to a default Th2 immune profile (Jankovic et al., 2001). Indeed, it is extremely unlikely that the immune system would rely on such a fragile, passive mechanism in situations where the Th2 response is linked to either immunopathology or pathogen clearance. In these settings, of which schistosomiasis provides a typical example, it is clear that active, instructive mechanism(s) of Th2 induction must exist to benefit both host and parasite.

The concept of default Th2 induction by DC has lingered because no immediately obvious DC-derived Th2-driving candidate has been described that is as clearly Th2 polarising as IL-12 in a Th1 setting. However, in the case of *S. mansoni* Ag, it is clear that there is an active requirement for CD40, OX40L and NF-κB1 expression by DC as a prerequisite for them to drive Th2 development (de Jong et al., 2002; MacDonald et al., 2002b; Artis et al., 2005). Further, the immune response induced by SEA-pulsed DC did not default to a Th1 response when SEA primed DC were transferred into an IL-4-deficient setting (MacDonald and Pearce, 2002a). Perhaps the single most compelling piece of evidence that exists to refute the default hypothesis in the context of pathogens is provided by experiments in which DC exposed simultaneously to SEA and the bacterium *Propionebacterium acnes* retained SEA-specific Th2 inductive ability (Cervi et al., 2004). For this to be able to occur, there must be active mechanisms of Th2 induction by DC. Defining the identity of (potentially novel) positive signals that promote Th2 development by DC is currently a major objective in the field.

While the identity of positive signals for Th2 development remain elusive, several reports have clearly illustrated the capacity of SEA to impart negative signals that may regulate Th1 inducing capacity of DC. SEA not only fails to conventionally activate DC but appears to down-regulate expression levels of some genes, as well as interfere with TLR-mediated signaling in response to a variety of TLR ligands including *Escherichia coli* LPS, *P. acnes,* CpG, poly I:C and soluble *Toxoplasma gondii* Ag (Agrawal et al., 2003; Kapsenberg, 2003; Zaccone et al., 2003; Cervi et al., 2004; Jankovic et al., 2004; Kane et al., 2004). Schistosome Ag interfere with TLR-initiated MAPK and NF-κB signalling (Kane et al., 2004), while also inducing specific transcription factors such as c-Fos that could be involved in the suppression of TLR-mediated conventional maturation pathways within the DC (Agrawal et al., 2003). SEA also appears to interfere with the ability of DC to promote CD4 + T cell progression through the cell cycle (Jankovic et al., 2004). Some of these inhibitory effects are likely to be in part due to the fact that SEA promotes TLR ligand-induced production of IL-10, although SEA inhibits TLR-initiated DC activation even in situations where IL-10 is absent (Kane et al., 2004). These examples likely represent only the tip of the iceberg in this area, since microarray analyses have shown IL-10-independent effects of SEA on the expression of over 100 TLR ligand-regulated genes (Kane et al., 2004). Whether this occurs as a result of SEA binding to TLR or alternative PRRs that initiate anti-inflammatory pathways has yet to be determined. However, it is important to note that the ability of SEA to interfere with conventional DC maturation is transient, with exposed cells regaining full activation potential within 6–12 h after exposure to SEA (unpublished observations). This transient effect suggests that the purpose of schistosome Ag interference with TLR-mediated pathways of DC activation is to limit potentially damaging Th1 development, rather than as a mechanism required for Th2 induction. In the case of schistosomiasis, this may be particularly important during the transit of eggs from the vasculature across the tissues and into the gut, where an inflammatory Th1 response against gut bacteria might be particularly undesirable.

6. Conclusions

It is clear that schistosomes fail to conventionally activate DC either in vitro, or during active infection . Irrespective of this (and contrary to prevailing dogma) these DC can capably stimulate naïve T cells, and drive then towards a Th2 phenotype. Based on our initial studies with SEA, we originally

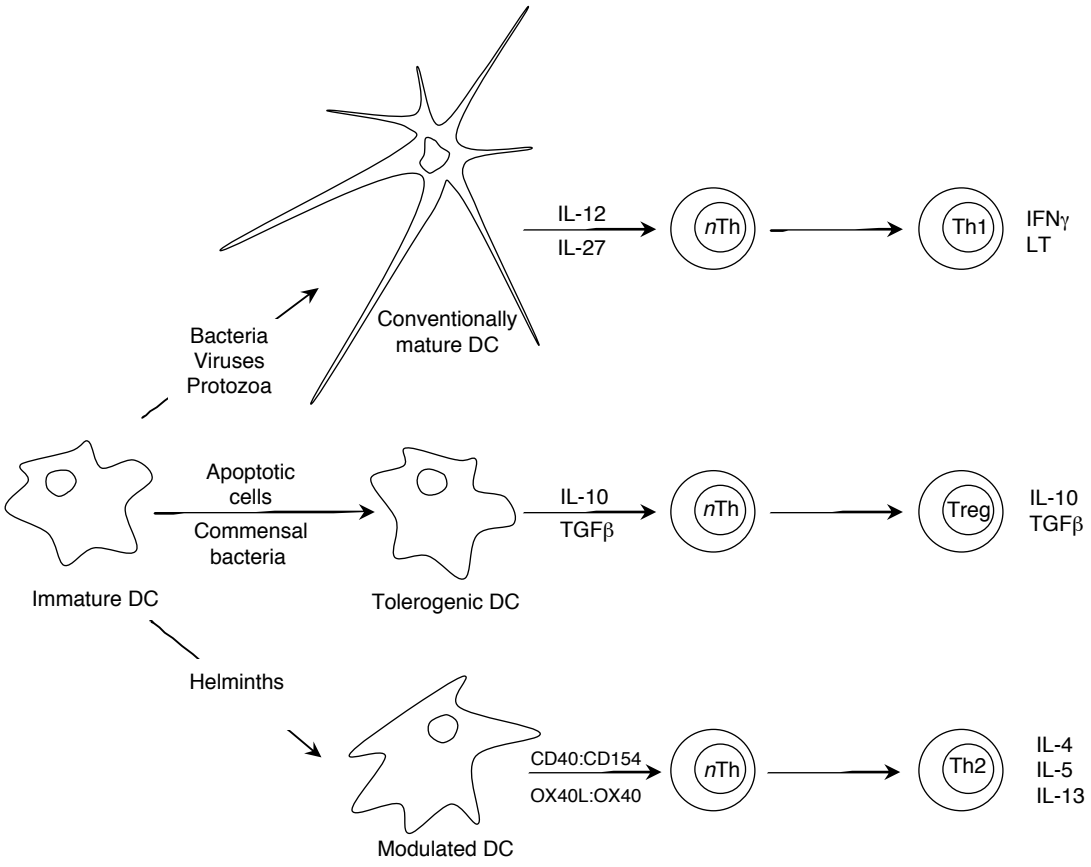

Fig. 1. Plasticity of dendritic cell (DC) function is determined by the type of stimulus encountered. Pathogens such as bacteria, viruses and protozoa generally activate dendritic cells conventionally and drive Th1 polarisation. In contrast, DC exposed to helminths show only minor signs of maturation, yet are capable at inducing development of Th2 response. Tolerogenic DC, generated by exposure to self antigen in the form of apoptotic cells or commensal bacteria, also fail to show signs of conventional maturation. It is likely that both Th1 and Th2 polarising pathogens also contain pathogen associated molecular patterns that can generate tolerogenic DC. TGFβ, transforming growth factor β; IFNγ, interferon γ; Treg, regulatory T cell.

proposed that a lack of conventional DC activation might be a feature of DC responses to schistosomes, and perhaps other helminths and Th2 development in general (MacDonald et al., 2001). Subsequent studies have provoked a reassessment of this original idea since certain life cycle stages of *S. mansoni*, as well as gastrointestinal nematodes such as *Nippostrongylus brasiliensis* (Balic et al., 2004) and *Trichuris muris* (Richard Grencis, personal communication) appear to activate DC more extensively than SEA does. What is clear is that none of the helminth Ag that have been assessed so far activate DC conventionally, highlighting that a modulated activation status does appear to be a general feature of helminth interaction with DC (Fig. 1).

An important conclusion that can be drawn from the literature is that induction of Th2 responses by schistosome-exposed DC does not occur by default, requiring active expression of specific costimulatory (CD40 and OX40L) and signaling (NF-κB1) molecules. Surprisingly, neither IL-4 nor IL-10 expression by DC is required for Th2 induction to schistosome Ag. It remains to be seen whether DC must express additional, as yet undefined, molecules that are critical for initiation and direction of a Th2 response against the parasite and whether the ability of schistosome Ag to interfere with TLR-mediated activation of DC is important for Th2 induction and development.

In a relatively short period of time, our understanding of how DC respond to schistosomes in vitro has increased dramatically, and is providing fundamental information on DC biology. Further work in vivo should prove valuable in determining the relevance of in vitro results, and in defining the importance of location in the process of DC activation and function in response to schistosomes. The liver and gut are the main sites of Ag exposure for eggs, whereas skin and lungs for larvae and vasculature for adults provide the major site of interface between the parasite and the immune system. Defining how DC interact with the parasite, and the potential network of other innate and adaptive immune cells at these diverse locations within the host, is an exciting goal. There is undoubtedly much that remains to be discovered in this area, with the hope being that a more complete comprehension of DC function might enable rational design of treatments and/or therapeutics against schistosomiasis or indeed any condition or disease that develops when the immune response is ‘unbalanced’.

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