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## Modulation of the host's immune response by schistosome larvae

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### SUMMARY

Schistosomes appear to have evolved several strategies to down-regulate the host's immune response in order to promote their own survival. For the host, down-regulation is also beneficial as it can limit the extent of pathology. It is widely accepted that schistosomes modulate the immune response during the chronic phase of infection after egg deposition has started. However, there is increasing evidence that modulation of the immune response can occur much earlier at the time infective cercariae penetrate the host skin. In this review, we explore the various lines of evidence that excretory/secretory (ES) molecules from cercariae down-regulate the host's immune response. We highlight the immunological factors that are produced and may be involved in regulating the immune system (e.g. IL-10, and eicosanoids), as well as speculating on possible mechanisms of immune modulation (e.g. mast-cell activation, T-cell apoptosis, and/or the skewed activation of antigen-presenting cells [APCs]). Finally, we draw attention to several molecules of schistosome origin that have the potential to stimulate the regulatory response (e.g. glycans) and link these to potential host receptors (e.g. TLRs and C-type lectins).

### Keywords

cytokine; helminth; immunomodulation; schistosomes

### BACKGROUND

Like many helminth parasites, schistosomes are long lived and can survive in the vertebrate host without causing severe manifestations of disease. It has been estimated that adult schistosome worms can remain in the human host for up to 40 years and each adult worm pair can produce 300 (*Schistosoma mansoni*) to ~3500 (*Schistosoma japonicum*) eggs per day (1), representing a significant antigenic insult to the host's immune system. The main manifestation of schistosomiasis is the granulomatous response to eggs trapped in host tissues such as the liver, intestines or bladder wall. However, pathology is largely chronic in nature with less than 5% of infected individuals suffering severe disease (2). Therefore, it appears that the host–parasite interaction has evolved to allow continued transmission of the parasite but also to limit severe pathology that may result in the death of the host.

Many studies clearly demonstrate that the chronic phase of infection is characterized by a state of immune hyporesponsiveness exhibited as a reduced ability of host cells to proliferate and a reduction in the size of the granulomatous lesions around embolized ova (2-4). Several

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excellent articles have recently focused on reviewing the evidence for immune modulation induced by the egg and discuss the different possible mechanisms of action (5-7). Notwithstanding egg-induced immune modulation, there are an increasing number of reports showing that immune regulation begins before egg deposition and that schistosome larvae from the point of infection in the skin are the first stage of the parasite to interfere with the host's immune-defence mechanisms. In this review, we examine the available evidence on the immunoregulatory nature of antigens released from infective larvae as they penetrate the host. This information shows that the released antigens not only stimulate innate immune cells but are also effective at limiting various host immune responses. We draw attention to a number of possible strategies and speculate on the mechanisms that could be used to effect modulation of the immune response, thereby improving the chances of survival of the invading parasite.

### Modulation of the host response *in vivo* by cercariae and skin-stage larvae

Infective schistosome cercariae gain entry to the mammalian or avian host via a percutaneous route and use a number of proteolytic enzymes to digest a route through the skin prior to their exit via blood capillaries or lymphatic vessels (8,9). Ordinarily, schistosomes traverse the skin of their primary host within days, and the vast majority enter the circulation to reach their final site of parasitization. A schematic diagram of schistosome migration through the skin is shown in Figure 1. The precise amount of time larvae spend in the skin has recently been debated (9-11), although evidence from tracking studies of *S. mansoni*, using both rodent (12) and primate (13) models, show that migration out of the skin can occur within 48–72 h, with the epidermal basement membrane providing the major obstacle for larvae to negotiate. The rate of *Schistosoma haematobium* migration resembles that of *S. mansoni*, although larvae of *S. japonicum* are faster to reach the dermis; in all cases the majority successfully leave the skin (14,15). In contrast, only a minority of bird schistosome *Trichobilharzia* larvae leave the skin site of infection of either the natural avian (16) or the mammalian host (17). Moreover, evidence from mice repeatedly exposed to *Trichobilharzia regenti* shows that migration of larvae from the skin is more compromised compared to a single exposure (17), and this occurs via an immune-dependent mechanism (18).

While exposure to a small number of cercariae may result in no more than a localized brief inflammation of the skin (19), repeated exposure to *S. mansoni* (A.P.M.; unpublished data) or *T. regenti* (17), causes marked cercarial dermatitis. Recent investigations of the inflammatory response in the skin using murine models of exposure to normal and radiation-attenuated (RA) *S. mansoni* larvae (19-22), or *T. regenti* (17), reveal that the induction of a heterogeneous influx of polymorphonuclear and mononuclear immune cells in the skin is orchestrated by a localized production of pro-inflammatory cytokines (e.g. IL-1 $\beta$ , IL-12, TNF $\alpha$ , MIP1 $\alpha$  and IL-6), as well as mediators with an immunoregulatory function (e.g. IL-10, prostaglandins [PG] E<sub>2</sub> and D<sub>2</sub>) (see Figure 1). Interestingly, a comparison of the three main species of *Schistosoma* that cause disease in humans shows that while *S. japonicum* induces a range of pro-inflammatory mediators, *S. mansoni* and *S. haematobium* appear only to elicit transcripts for IL-1 receptor antagonist (IL-1ra), IL-10 and TNF $\alpha$  (14). This suggests that there are differences in the induction of pro-inflammatory compared to regulatory mediators, with species that migrate more slowly through the skin favouring the induction of inhibitory IL-1ra and IL-10. Combined, all of the above studies indicate that an innate inflammatory immune response occurs in the skin within hours of cercarial penetration but there is also evidence for the early production of immune regulatory mediators.

## Induced immune mediators with regulatory activity

Chief among soluble mediators with known immunoregulatory function and found to be induced early after exposure to schistosome cercariae is IL-10 (14,20,21,23 and see Figure 1). This cytokine has wide-ranging regulatory effects upon antigen presentation, costimulation and the development of acquired T-cell responses (24). Interestingly, RA cercariae, which induce high levels of protective immunity in mice, either fail to induce IL-10 production (19) or elicit a delayed response relative to normal larvae (21). The secretion of IL-10 also occurs later than that of other pro-inflammatory cytokines (e.g. IL-12 and IL-1 $\beta$ ), suggesting that it acts to limit their effects (21). This observation is supported by studies using IL-10-deficient mice that have an enhanced inflammatory response in the skin (19,22), coincident with elevated expression within the skin of pro-inflammatory cytokines and MHC II and CD86 (22). These mice also have enhanced Th1-type responses (22,25) and greater levels of immunity when exposed to multiple doses of RA cercariae (25).

It appears that IL-10 is one of the key regulatory mediators of immune responsiveness in skin, especially after exposure to multiple doses of cercariae. We noted that IL-10 production by cells in murine skin was highly elevated after multiple exposures to *T. regenti* (17) cercariae. The immediate production of IL-10 within 1–3 h of re-exposure suggests it exists in a preformed state but, as yet, a cellular source in the skin has not been identified. Ramaswamy *et al.* (19) report that keratinocytes are an important source of IL-10, but other potential sources include macrophages, dendritic cells (DCs) or even B1 lymphocytes. Given the recent interest in ‘natural’ CD25<sup>+</sup>CD4<sup>+</sup> regulatory cells (26) and ‘induced’ regulatory CD4<sup>+</sup> cells (27), these too are a likely source of IL-10 in the skin, particularly since the number of CD4<sup>+</sup> cells increases with time after schistosome infection and after multiple exposure to *T. regenti* (17) or *S. mansoni* (A.P.M.; unpublished data). Indeed, CD4<sup>+</sup>CD25<sup>+</sup> cells have been identified as an important feature of the skin of mice that harbour a persistent *Leishmania major* infection (28). The predicted presence of regulatory T cell involvement, even at this early stage, raises the possibility that TGF $\beta$  might also have a modulatory role since production of this cytokine is a hallmark of some T regulatory cells (29). However, at present there is no evidence for, or against, its involvement during early skin phases of parasite migration.

Another group of inhibitory molecules produced after exposure to schistosome larvae are eicosanoids of parasite and/or host origin (19,20,30,31 and see Figure 1). Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) can function via a cyclooxygenase 2-dependent pathway to aid the production of IL-10 (32) and has been proposed as the prime mediator of schistosome-induced immunoregulation in the mouse skin (19). However, others instead highlight a role for schistosome-derived PGD<sub>2</sub> as a factor involved in the IL-10-independent inhibition of host Langerhans cell (LC) migration (20). The inhibitory function of PGD<sub>2</sub> is mediated through the membrane-bound prostanoid receptor 1 (DP1), which is expressed on LCs. The migration of LCs as antigen-presenting cells (APC) from the site of schistosome exposure to the draining lymphoid tissue is likely to be important in the subsequent priming of antigen-specific CD4<sup>+</sup> responses. Therefore, interruption of the movement of these cells represents a special strategy of the parasite to modulate the host's immune response.

Although various different eicosanoids probably have roles in regulating dermal inflammation, several other mediators may play supporting roles in securing the dominance of immune regulation in the skin. One molecule long known to inhibit the pro-inflammatory functions of IL-1 is IL-1ra. It is produced by human keratinocytes in response to excretory/secretory (ES) products of schistosome larvae (33), although infection of the murine skin does not increase the expression of its transcript (20). It is even possible that an abundance of IL-12p40, rather than acting in concert with p35 as a pro-inflammatory p70 heterodimer (or with p19 as IL-23), may be present in excess as the inhibitory p40 homodimer (34).

Together, the above studies show that there are multiple mediators of immune regulation present at the site of parasite exposure. It is likely that all play a role in modulating the host's immune reaction to the invading parasite, possibly as part of a highly coordinated mechanism that has yet to be fully dissected.

### Molecules of larval origin with immunomodulatory function

Evidence that schistosome larvae can induce a state of immune regulation in the skin raises the question as to the identity of the parasite molecules responsible. Invasive cercariae and schistosomula in the skin provide the source of stimulatory and inhibitory molecules, particularly those derived from the glycocalyx and released as proteases to aid skin penetration by the parasite (35). ES products of schistosome cercariae, specifically those released by the transforming larvae, are rich in components of the glycocalyx and secretions from the pre- and post-acetabular glands. Most of the glycocalyx is lost by cercariae at infection (35,37), but some of its components remain associated with schistosomula for a period of time after transformation (15,37). The acetabular glands are the source of serine proteases with elastase-like activity, which degrade macromolecules in the skin, thus aiding penetration and migration (9,38); further proteases released from the head gland of skin-stage schistosomula may be responsible for penetration of the basement membrane and the underlying dermis (10).

The immunomodulatory effects of ES products of various helminths has long been realized (39), although relatively few reports have focused on the modulatory effects of ES products released by schistosome cercariae, or the newly transformed larvae. Nevertheless, Vieira *et al.* (40) were one of the first to report that material released from cercariae could inhibit the *in vitro* proliferation of human peripheral blood mononuclear cells (PBMCs) from schistosome-infected patients in response to adult worm antigens or to mitogen. The released cercarial preparations also inhibited the response of naïve PBMCs to mitogen. Moreover, when antigen preparations of equal protein concentration from different stages of larval development were compared, it was found that ES products released within the first 3 h of cercarial transformation (termed 0–3 hRP) was less stimulatory (in terms of lymph node cell proliferation) than soluble preparations of whole larvae (41).

Several studies have shown that cercarial ES products when used to immunize naïve skin lead to an oedema and influx of neutrophils (42,43) but it was unclear whether this inflammation was beneficial to the host or the parasite. In fact, although clear evidence for the induction of inflammation was apparent, it was also noted that survival of a secondary infection with cercariae, over the same skin site, was significantly enhanced and this was related to the proteolytic activity of the ES products (43). The same enhancement of adult worm burden was observed following intradermal injection of cercarial 'glycocalyx' (44). Combined, these observations could be interpreted to suggest that products of cercariae (proteases and/or glycocalyx) have the ability to modulate the immune response and promote parasite survival, rather than induce host-protective immune mechanisms.

In future studies, it will be important to consider immune regulation at the level of whole tissue (i.e. the skin site of infection) and in relation the rest of the immune circulatory system. However, at this point, progress towards identifying putative parasite ligands of immune regulation have tended to focus upon individual cell types, as will now be discussed.

### Activation of mast cells by larval antigens?

The functional role of the *Schistosoma* ES preparation termed 0–3 hRP released by transforming larvae has been explored using a number of different cell types that might be

expected to occur naturally in the skin. For example, ES products are a potent inducer of *in vitro* mast-cell degranulation and the production of IL-4, histamine and 5-hydroxytryptamine in an IgE-independent manner (45). This mirrors some of the soluble mediators released by the skin after *T. regenti* infection (17) and supports earlier studies reporting the release from *S. mansoni* cercariae of a mast cell-triggering factor (46). Although the active molecule(s) has not yet been identified, the ability of schistosome 0–3 hRP to stimulate mast cells is thought to be dependent upon the presence of proteases (45) that are widely known to be important allergens. One candidate molecule might be the schistosome homologue of the human translationally controlled tumour protein (TCTP), which can activate basophils/mast cells (47). Although histamine is generally thought to help activate APCs via increased cytokine production and costimulatory molecule expression (48,49), binding of the H2 histamine receptor inhibits IL-12 (50) thus presenting one way by which activated histamine-producing mast cells regulate the immune response, through the induction of IL-10 (51).

### Lymphocyte apoptosis?

Another strategy used by a number of parasites to regulate the host's immune response is parasite-induced apoptosis of host cells (52). One can appreciate the advantage of such a strategy in that the helminth parasite could induce the death of potentially 'dangerous' host immune cells and thus subvert the host's attempt to kill the worm or develop a protective acquired response. In schistosomes, a molecule termed '*S. mansoni* apoptosis factor' (SMAF: rMW 23 kDa) has been identified, which induces apoptosis specifically in the CD4<sup>+</sup> lymphocyte population via a Fas–FasL interaction (53). This molecule was found to be a significant component of cercarial ES products and substantially reduced the viability of cells from the skin-draining lymph node during *in vitro* coculture; *in vivo* analysis also demonstrated apoptotic cells surrounding invading larvae in the skin (53). These authors suggest that apoptosis of CD4<sup>+</sup> cells modulates the host immune responses to allow larvae to escape detection and may be partly mediated by IL-10. As such, it would be interesting to assess the effect of SMAF on regulatory CD4<sup>+</sup> cells. Moreover, these authors report that RA larvae do not express this molecule, providing one explanation for why RA larvae are more efficient at stimulating host protective immunity than normal ones.

### Skewing the activation of APCs?

Recent studies have focused upon the immune activating and regulatory functions of cercarial ES with respect to potential APCs. Activation of APCs that prime for particular Th phenotypes that are beneficial to the parasite may be a subtle form of immune regulation, and in the context of a single exposure to RA *S. mansoni* larvae, there is a consensus in the murine model that Th1 cells can mediate an antiparasite host protective response against larval stages (8,54). Recently, we reported how 0–3 hRP activates bone marrow-derived DC by up-regulating limited expression of MHCII, CD40 and CD86, and inducing the release of pro-inflammatory IL-6 and IL-12p40 but not regulatory IL-10 (55). Moreover, DC activated with 0–3 hRP prime CD4<sup>+</sup> cells to secrete abundant IL-4, IL-5 and IL-10 *in vitro* and *in vivo* indicative of a strong Th2-type phenotype (55). As such, DCs primed with 0–3 hRP resemble those stimulated with SEA (schistosome soluble egg antigen (56,57)) because both drive dominant Th2-type responses. The tendency of DC stimulated with helminth products to promote Th2 responses may reflect their inability to produce Th1-promoting cytokines like IL-12, IL-23 and IL-27 (56). In this respect, neither 0–3 hRP nor SEA induces abundant IL-12p70, unlike 'Th1-inducing' LPS, and *Propionibacterium acnes* (55,56). However, it seems unlikely that the DC is simply not activated by 0–3 hRP, but rather a 'modified' maturation state is induced with the limited up-regulation of certain cytokines, MHC II and costimulatory molecules (i.e. CD40 and CD86, but not CD80 or OX40L) (55). We are currently performing proteomic analyses of DCs activated with 0–3 hRP to define the

'modified' phenotype and identify 'hallmarks' of DC primed with 0–3 hRP in comparison with other Th1- and Th2-activating agents (Ferret-Bernard and Mountford, unpublished data).

The role of CD40–CD154 interaction appears critical to the function of DCs to promote Th2-type responses, as shown by studies using DCs stimulated with Th2-inducing SEA (56,80). We show that the Th2-type responses induced by DCs primed with 0–3 hRP are dramatically altered to a Th1 phenotype by the ligation of CD40 using anti-CD40 antibodies (55). This reversal of phenotype is concurrent with a substantial increase in the secretion of IL-12. However, we have also observed that IL-12 production by skin biopsies within the first few days of parasite exposure are not completely ablated in CD154<sup>-/-</sup> mice (Hewitson, Hamblin and Mountford, in prep.). This indicates there are different routes leading to the release of Th1-inducing cytokines, and therefore by analogy there are probably multiple pathways by which cercarial ES products skew the phenotype of DCs such that they promote Th2-type responses.

The 'modified' DC, or APC, may exist in a state of pathogen-induced suppression to other unrelated microbial products (56). This is observed in DC to occur in response to SEA (58), and we found that optimal doses of 0–3 hRP inhibits IL-12p40 cytokine production by macrophages stimulated with the microbial products LPS or Zymosan A (S. J. Jenkins, unpublished data). This supports an immunomodulatory role for molecules within cercarial ES products. However, in the same experiment, levels of IL-6 and IL-10 were increased, and in studies on DCs, 0–3 hRP increased the secretion of IL-12 in response to CD154-transfected fibroblasts (55). This indicates that 0–3 hRP has differential effects on DCs and macrophages, perhaps as a result of the expression of different surface innate immune receptors (see succeeding discussions). One explanation, as proposed for SEA (58), is that the intracellular fate of the schistosome molecules differs from other pathogen molecules, or even between molecules that comprise the heterogenous mixture of 0–3 hRP. This raises the question as to the identity of host receptor(s) that bind one, or more, of the molecules that comprise 0–3 hRP.

### Host receptors involved in recognition of cercarial ES products

Studies using thioglycollate-elicited peritoneal macrophages activated with 0–3 hRP demonstrate that cytokine production (IL-6, IL-12p40) is entirely MyD88-dependent indicating that activation of host cells by 0–3 hRP occurs via a toll-like receptor (TLR)-dependent mechanism (81). In contrast, this study also shows that although IL-12p40 and IL-10 production was largely dependent upon the presence of functional TLR4 (using C3H/HeJ and TLR4<sup>-/-</sup> mice), the production of IL-6 was largely TLR4 independent, suggesting that different receptors are involved. *In vivo* studies, however, show that IL-12p40 production in the skin in response to invading larvae is not entirely dependent upon functional TLR4 (21). A separate role for TLR2 ligands within 0–3 hRP has not yet been established, although lipids from schistosome eggs are TLR2 ligands and drive DCs to produce IL-10 (59). The differential response in cytokine production between mice deficient in TLR4 further supports the likelihood that 0–3 hRP is comprised of different molecules with contrasting receptor specificities on host innate immune cells and on APCs in particular.

The involvement of TLR4 would initially suggest the activation of pro-inflammatory cytokine production as occurs following ligation with bacterial products like LPS (60). However, a recent report has identified dextran-conjugated lacto-N-fucopentaose III (LNFPIII) as a glycoconjugate that can ligate TLR4 but suppresses IL-12 production by DCs (61). LNFPIII is a pentasaccharide that terminates in Lewis<sup>X</sup>, which in turn is a trisaccharide that occurs on glycoproteins and glycolipids of schistosomes. DCs activated with LNFPIII

prime DCs, which drive Th2-type responses (61) albeit in a MyD88-independent manner (62). However, DCs activated with lacto-neotetraose (LNT), a tetrasaccharide that does not have  $\alpha$ 1,3-linked fucose found in LNFPIII, do not drive Th2-type responses (61). It appears that multivalent Lewis<sup>X</sup>/LNFPIII has a strong propensity to modulate the immune response through the induction of IL-10 by PBMC and B-1 cells (63,64). Immunomodulatory molecules that express Lewis<sup>X</sup>, as well as various other fucose-containing glycan elements (e.g. core  $\alpha$ 1,3-linked fucose and difucosylated LDN), have been isolated from the schistosome egg (62,65-67). Lewis<sup>X</sup> is also present at other different life cycle stages, including cercariae, as are LDN, LDN-F and many other immunogenic glycans (68-72). This raises the possibility that glycans expressed by cercariae or skin-stage larvae also have immunomodulatory activity.

Glycans in the cercarial ES products could bind cell surface C-type lectins such as DC-specific ICAM-3-grabbing non-integrin (DC-SIGN), or the mannose receptor (MR), which in turn modifies the activation of TLRs (73). Both of these C-type lectins are conventionally associated with endocytosis of pathogen-associated material, whereas ligation of TLRs leads to APC activation and the initiation of gene (e.g. cytokine) transcription. Binding of pathogen glycans expressing mannose, fucose or Lewis<sup>X</sup> to DC-SIGN on immature DCs can lead to the induction of tolerance (74,75), and interestingly, DC-SIGN binds to schistosome egg antigens (75,76). The binding of ligands to the MR is reported to stimulate IL-10 and IL-1ra release by DCs that inhibit the induction of Th1 responsiveness, and instead favour the amplification of Th2 circuits (77). In this context, an Fc chimeric protein of the MR (78) has identified an abundance of MR ligands in the glycocalyx compartment of 0–3 hRP that is stimulatory of IL-10 production by macrophages (81, and S. J. Jenkins, unpublished data).

Finally, as an intriguing endnote, researchers have now identified the parasite-derived factor responsible for the observed reduced migration of LCs after exposure to normal cercariae (20). This has been revealed to be the schistosome vaccine candidate glutathione S-transferase that has PGD<sub>2</sub> synthase activity (79). This is a further illustration of how the parasite can use its own molecules to promote immune regulation at the earliest point after infection but also shows that an individual molecule can have contrasting effects on the host's immune response.

## CONCLUSIONS

Compared to studies on immune regulating activities promoted by the schistosome egg, less is known about the modulatory activities of cercarial ES products. In the above treatise, we summarize the current state of knowledge and describe how immune modulation appears to be operational well before egg deposition occurs. The immunomodulatory actions of invading cercariae are concentrated among those molecules released by the larvae as it penetrates the host skin (e.g. among the glycocalyx and acetabular secretions). The ultimate goal of such activity appears to be the down-regulation of host protective immune responses, and therefore enhance the ability of schistosome larvae to exit the skin en route to their final sites of maturation. Central roles for pro-inflammatory IL-12 and regulatory IL-10 underpin the immune reaction, but other molecules (i.e. eicosanoids) undoubtedly have supporting roles through specific mechanisms (e.g. inhibition of LC migration or of lymphocyte apoptosis). We conclude that the ES products of schistosome cercariae must contain a number of different ligands that can each activate or modulate the host's innate immune system through coordination, or cross talk, between the binding of different TLRs and C-type lectins. Although the biochemical characterization of the parasite ligands of such receptors is at an early stage, it is likely that there will be multiple candidates that will allow for a complex but highly evolved strategy to promote parasite survival in the primary host.

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## Abbreviations

<b>0–3 hRP</b>	products released by larvae 0–3 h after transformation
<b>APC</b>	antigen-presenting cell
<b>DC</b>	dendritic cell
<b>DC-SIGN</b>	DC-specific ICAM-3-grabbing nonintegrin
<b>ES</b>	excretory/secretory
<b>LC</b>	Langerhans cell
<b>MR</b>	mannose receptor
<b>PBMC</b>	peripheral blood mononuclear cell
<b>PG</b>	prostaglandin
<b>RA</b>	radiation-attenuated
<b>TLR</b>	toll-like receptor

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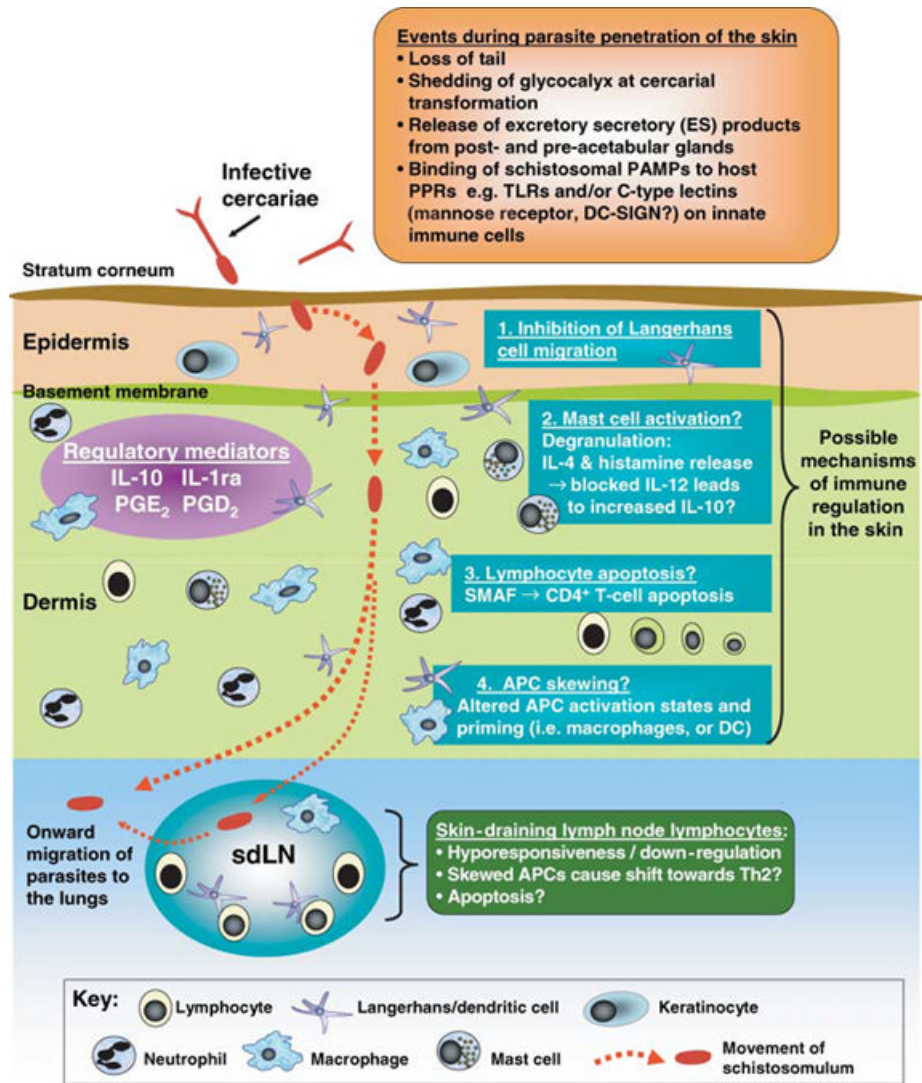


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**Figure 1.**

A schematic diagram showing the generalized pattern of schistosome migration through the skin, and the possible mechanisms of immunoregulation that might operate in this tissue. Full details of the regulatory mediators released by both the parasite and the host are given in the main text of the review, as are descriptions of the possible mechanisms of immune regulation and identities of probable ligands. The diagram encompasses data obtained from studies of different *Schistosoma* and *Trichobilarzia* species with specific references given in the main text.