

Control of inflammatory diseases by pathogens: lipids and the immune system

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Inflammatory diseases such as asthma and diabetes are rising in industrialized countries and the modern lifestyle that is associated with lower exposure to microbes has been held responsible for the increasing prevalence of these diseases. Several studies have shown an inverse association between pathogen-exposure and allergy or autoimmunity. The mechanisms behind such protective effects have been investigated at the epidemiological, cellular and molecular level and have provided data on the ability of lipids either derived directly from pathogens or up-regulated as a result of an infection to down-regulate immune responses and thereby control inflammatory diseases. In this mini-review, recent findings and new concepts relating to the immunosuppressive effects of endogenous lipids and those encountered upon exposure to bacteria, protozoa and particularly helminths are discussed. The overview focuses on the modulation of interactions between the antigen-presenting compartment and T cells to start an anti-inflammatory “program” with potential to regulate disease processes.

Key words: Helminth / Lipid / Immunoregulation / Dendritic cell / Hygiene hypothesis

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1 The inverse relationship between infections and allergies

The prevalence of allergies has increased significantly over the last few decades, particularly in industrialized countries. Within these countries, a negative association has been found between certain childhood infections and allergic diseases [1, 2]. Lifestyles such as anthroposophy or traditional farming — thought to be associated with higher exposure to pathogens or pathogen-derived products — have been shown to be protective against atopic disorders [3, 4]. Furthermore, in low-income countries, where exposure to pathogens is higher, the prevalence of allergy is often lower than in industrialized countries [5]. Studies examining the relationship between allergies and parasitic infections in areas where transmission is intense have revealed that children with chronic helminth infections have a lower risk of wheeze or of skin-prick-test positivity for house-dust mite [6, 7].

The question of how infections can prevent allergies has received much attention in the last few years. Although many bacteria and viruses induce Th1 responses, which in turn may prevent the development of Th2 responses, helminths — which are potent Th2 inducers — are surprisingly also protective [7]. This has led to the question of what additional mechanisms, acting downstream of the induction/initiation phase, suppress allergic inflammation. Such mechanisms downstream of T cell polarization would work to protect not only from Th2 inflammation but also from Th1 inflammation, and their absence would explain the concurrent rise at the population level in allergies (Th2 diseases) and autoimmunities (often Th1 diseases) [8]. The possibility that immunosuppressive regulatory responses stimulated during repeated/intense exposure to pathogens or pathogen-derived products protect against inflammatory diseases has received much attention [9, 10]. Indeed, intense exposure to bacterial LPS [11] as well as chronic helminth infections (during these infections the immune system is challenged relentlessly with foreign antigens) leads to some degree of immune tolerance (van der Kleij et al., unpublished data).

The mechanisms behind the observed immune hyporesponsiveness seen as a result of intense exposure to environmental LPS have yet to be elucidated. However, the hyporesponsiveness to antigen-specific and polyclonal stimuli in chronic helminth infections seems to be

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Abbreviations: 15dPGJ₂: 15deoxyΔ^{12,14}PGJ₂ **Lyso-PA:** Lysophosphatidic acid **Lyso-PC:** Lysophosphatidylcholine **Lyso-PS:** Lysophosphatidylserine **LXA4:** Lipoxin A4 **TLR2:** Toll-like receptor 2 **Treg cell:** Regulatory T cell

associated with IL-10 and TGF- β — immunosuppressive cytokines that are characteristically secreted by antigen-presenting cells and regulatory T cells (Treg cells).

Treg cells, which are able to control immune responsiveness, were identified recently in patients with chronic asymptomatic helminth infections [12]. Treg cells that were cloned from onchocerciasis patients expressed high levels of cytotoxic T lymphocyte antigen 4 (CTLA-4) and IL-10 [13]. In addition, filaria-infected patients were shown to have elevated frequencies of CTLA-4-expressing T cells, which are mainly present in the CD4⁺CD25⁺ T cell population. Furthermore, in experimental models of filarial infection, the neutralization of Treg cells by antibodies either directed to CD25 (Gillan and Devaney, unpublished) or to GITR (Taylor, Allen and Maizels, unpublished) resulted in a significant increase in T cell proliferation and cytokine production. Therefore it is likely that Treg cells are important for T cell hyporesponsiveness seen in chronic helminth infections. Several studies have shown that this hyporesponsiveness can extend to third-party antigens. After routine BCG or tetanus vaccination, cell-mediated immune responses were lower in helminth-infected subjects [14, 15]. The precise mechanisms whereby Treg cells suppress responses to parasite antigens and third-party antigens have yet to be clarified.

Given that helminths are such potent inducers of immune hyporesponsiveness, it is conceivable that these organisms form a rich source of immunomodulatory molecules that may be of potential use to combat inflammatory diseases such as allergies and autoimmunities. Indeed, in a model of food allergy, the presence of a gut helminth significantly diminished levels of allergen-specific IgE and anaphylactic symptoms [16]. In autoimmunity, extracts of eggs and adult worms of *Schistosoma mansoni* were recently shown to be able to prevent the onset of type I diabetes in NOD mice [17].

With respect to exposure to bacteria and protozoa, and the inverse relationship with allergies, most data come from epidemiological and a few experimental studies. One elegant experimental study has shown that the suppressive effect of *Mycobacterium vaccae* on eosinophilic airway inflammation (in mice that were primed with ovalbumin) was related to the induction of Treg cells [18], supporting the proposition that the immunoregulatory network may also play an important role in the protective effect of infections, other than helminths, on allergic disorders.

2 Pathogen-derived and endogenous immunomodulatory lipids

2.1 Lessons from pathogens

Pathogens display a wide array of carbohydrates, (glyco)proteins and lipids that interact with the human immune system. Interestingly, our recent studies show that in schistosomes, lipids in particular are able to induce down-modulation of immune responses via the induction of Treg cells [19]. Traditionally, many immunologists regarded lipids as inactive molecules embedded in membranes that at the most could carry bioactive headgroups. However, it is becoming more and more evident that lipids themselves are important molecules involved in immune responses. Although immunological activity was first attributed to the polar headgroup of lipids, it is now becoming increasingly clear that the apolar lipid moieties of glycolipids, phospholipids, lipoproteins and lipopeptides have a profound influence on the biological activity of these molecules.

There are already several excellent reviews on the importance of lipids in the control of granulocytes during inflammation [20, 21]. In this review both endogenous and pathogen-derived lipids with immunomodulatory properties will be discussed, highlighting their anti-inflammatory activities on the antigen-presenting compartment and T cell responses (Fig. 1).

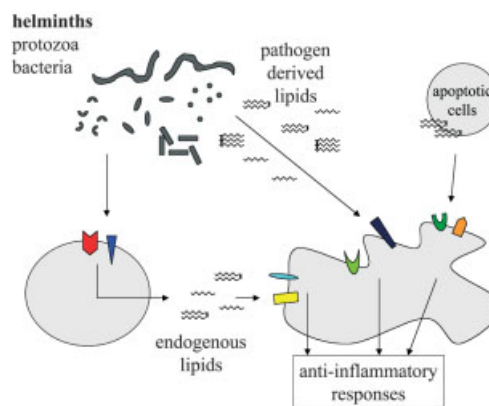


Fig. 1. Anti-inflammatory lipids: an overview. Pathogens can induce anti-inflammatory responses either directly by lipids that are present in the pathogen, or by inducing the production of endogenous lipid mediators in the host. Some pathogens can induce apoptosis of host cells; apoptotic cells, which expose phosphatidylserine in the outer leaflet of the cell membrane, in turn can switch immune responses into an anti-inflammatory mode.

2.2 Induction of endogenous immunomodulatory lipids by pathogens

The best-characterized immunomodulatory lipids are naturally occurring endogenous eicosanoids derived from the 20C poly-unsaturated fatty acid arachidonic acid, which is released from membrane phospholipids and converted by the action of cyclooxygenases and lipoxygenases. It is now generally accepted that eicosanoids such as leukotrienes and some prostaglandins have pro-inflammatory activity whereas other prostaglandins and lipoxins exert anti-inflammatory signals. Here we will focus on certain prostaglandins and lipoxins (Fig. 2) that have been reported to exert anti-inflammatory effects.

PGE₂, which can act through the G-protein-coupled receptors EP1, EP2, EP3 and EP4, is a potent inhibitor of cellular proliferation and regulates cytokine synthesis: it can inhibit IL-2 synthesis [22] and IL-2 receptor expression [23] on T cells. On antigen-presenting cells such as macrophages and DC it inhibits production of IL-1 [24], TNF- α [25] and IL-12 [26], whereas IL-10 production is increased [27]. In contrast, PGD₂, another prostaglandin for which anti-inflammatory effects have been reported, inhibits both IL-12 and IL-10 production by human DC [28]. PGD₂ can act through the DP receptor that is coupled to a G_{i/o}-type G protein, and can activate the CTRH2 receptor (chemoattractant receptor-homologous mole-

cule), a G_{ai}-type G protein that is selectively expressed on Th2 cells, basophils and eosinophils [29].

Prostaglandins were shown to be involved in the interaction of the parasite *Trypanosoma cruzi* with its host. High production of PGE₂ was found in spleen cells from *T. cruzi*-infected mice, and blocking prostaglandin production by inhibiting cyclooxygenase activity markedly increased lymphocyte proliferation and enhanced host mortality upon experimental infection with this protozoan parasite, although parasite levels were not affected [30]. Thus, production of prostaglandins is an important part of the host immune response, not to combat the infection *per se*, but rather to limit immune responses elicited by the parasite that would otherwise be destructive to the host. Parasites not only induce prostaglandin production by the host to suppress the immune response, but also are able to produce prostaglandins themselves. Schistosomes were shown to secrete PGD₂, thereby inhibiting the migration of Langerhans cells upon exposure to schistosome cercariae [31], and *Onchocerca volvulus* was shown to express glutathione S-transferase on its surface that produces PGD₂ directly at the host-parasite interface [32]. The question regarding helminths is whether PGD₂ production is involved in controlling anti-parasitic responses, which would justify the investment made by helminths to elaborate such anti-inflammatory molecules.

Another set of arachidonic-acid-derived molecules, termed lipoxins (lipoxygenase interaction products) are endogenous trihydroxytetraenes that are generated during inflammatory responses and are involved in the resolution of inflammation [33]. LipoxinA₄ (LXA₄; Fig. 2) is involved in limiting parasite-induced inflammation and mortality during chronic *Toxoplasma gondii* infection. *T. gondii* was shown to inhibit IL-12 production in DC by inducing LXA₄ generation [34], and mice deficient in 5-lipoxygenase, an enzyme critical for LXA₄ synthesis, are more susceptible to mortality from *T. gondii* infection [35]. This increased mortality was not the result of a higher parasite burden, but rather resulted from pro-inflammatory cytokine-induced tissue pathology. This indicates that LXA₄ is not involved in combating the parasite, but has an important role in keeping the cell-mediated immune effector responses under control to avoid excessive damage to host tissues [33]. The question of whether lipoxin induction is specific to *Toxoplasma* or represents a general anti-inflammatory feedback loop response to more pathogens needs to be investigated.

Related to this one should consider that lipoxin biosynthesis has been found in many human inflammatory diseases, including asthma. Interestingly, lipoxin levels were

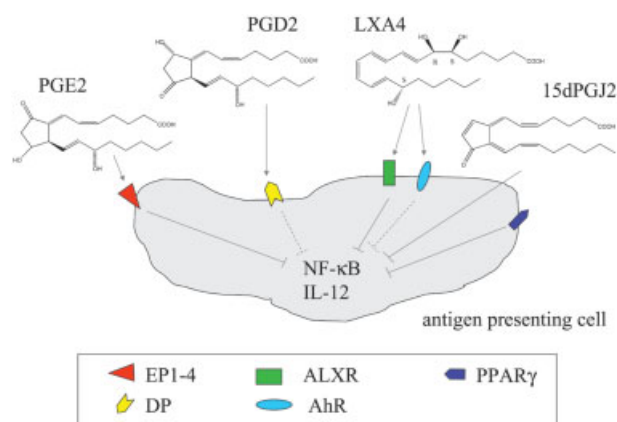


Fig. 2. Eicosanoids that act on antigen-presenting cells to inhibit inflammatory pathways. PGE₂, PGD₂, LXA₄ and 15dPGJ₂ act on receptors that have been shown (solid lines) or are thought (dotted lines) to inhibit NF- κ B activation and IL-12 production. As well as acting through peroxisome proliferator-activated receptor γ (PPAR γ), 15dPGJ₂ has been shown to inhibit NF- κ B activation and its binding to DNA independently of a receptor [69].

found to be higher in subjects with mild asthma compared with individuals with severe asthma [36]. Indeed synthetic lipoxin analogues have been shown to block the development of allergen-induced airway hyperresponsiveness and prevent expression of IL-5, IL-13, eotaxin and prostanoids [37].

LXA4 can act on the G-protein-coupled receptor designated ALXR, also referred to as formyl peptide receptor-like 1 (FPRL1) [38], to inhibit NF- κ B activation and inflammatory responses [39]. In addition, LXA4 can also activate the aryl hydrocarbon receptor (AhR) [40], which is a ligand-activated transcription factor that is present in the cytosol and upon ligand binding translocates to the nucleus, where it can activate responsive genes, most of which are involved primarily in xenobiotic metabolism. Persistent activation of the AhR has been associated with immunosuppression [40], but the mechanism remains to be elucidated.

2.3 Immunomodulatory lipids expressed by pathogens

Pathogens display a wide array of lipids and acylated proteins or peptides, and data on their importance in immunomodulation are only beginning to emerge.

Bacterial interaction with the immune system has been studied extensively at the level of the innate immune sys-

tem. It has become clear that the presence of lipid moieties in bacterial products is essential for recognition by some pattern-recognition receptors, particularly by Toll-like receptor 2 (TLR2), which can be activated by a wide variety of acylated bacterial ligands (Fig. 3). For example, mutants of cloned *Escherichia coli* lipoproteins that lack acyl lipid moieties were shown to be unable to activate TLR2 [41]. Increasing details are becoming available on specific structural motifs that are required for the interaction of lipids with the immune system.

Many TLR2-activating bacterial lipoproteins contain the characteristic N-terminal lipopeptide Pam3CysSerLys4 (PAM3CSK) (Fig. 3), which consists of three acyl chains, all essential for TLR activation [42]. The mycoplasmal lipopeptide MALP-2 (Fig. 3) differs from conventional bacterial lipoproteins in that it has a free N terminus. Thus, this structure contains only two ester-bound fatty acids, but nevertheless can potentially activate TLR2 [43]. For MALP-2 it has been shown that not only the presence of two fatty acids is essential for TLR2 activation, but also the configuration of the lipid moieties appears to be important: the R-stereoisomer of MALP-2 is a 100-times more potent TLR activator than the S-stereoisomer [44]. The situation is less stringent for TLR2 activation by lipoteichoic acid (LTA), a cell-wall component of Gram-positive bacteria. The lipid anchor of LTA is essential for biological activity, but the structural requirements appear to be less strict than for the bacterial lipopeptides discussed above: although the presence of two acyl chains

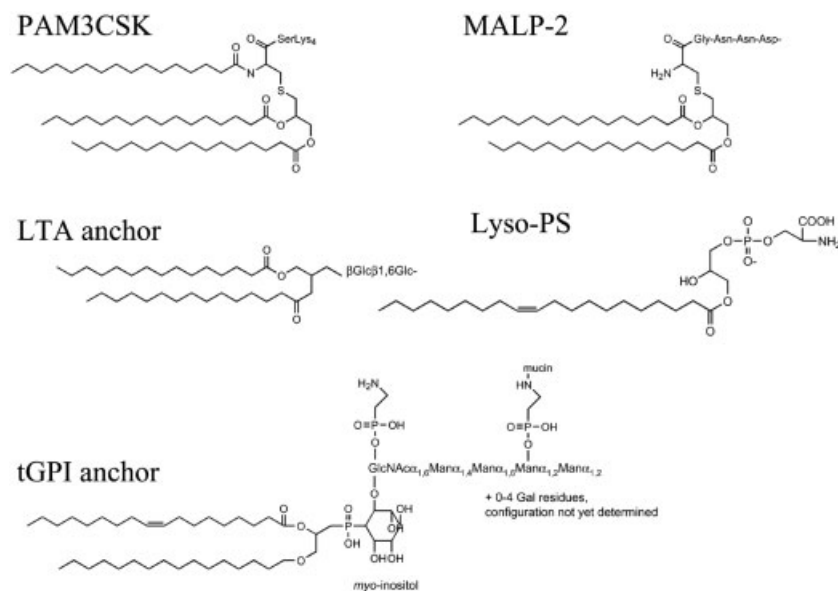


Fig. 3. TLR2-activating pathogen-derived lipids for which the importance of a lipid moiety has been demonstrated. PAM3CSK is the bacterial lipopeptide Pam3CysSerLys4. MALP-2 is a mycoplasmal lipopeptide. The lipoteichoic acid (LTA) anchor is present in Gram-positive bacteria. Schistosomal lyso-PS can have a C20:1 acyl chain. Finally, the tGPI anchor is present in *T. cruzi* trypomastigotes.

within the lipid anchor is required for optimal TLR activation, anchors with only one acyl chain are still able to induce production of inflammatory cytokines [45].

The variable number of acyl chains necessary for TLR2 activation may be linked to the finding that TLR2 is active as a heterodimer [46]. It was shown that TLR6 can function in association with TLR2 to confer responsiveness to MALP-2 [47]. In contrast, TLR2 activation by PAM3CSK was shown to require TLR1 but not TLR6 [48]. Thus, TLR6 seems to be essential for recognition of diacylated lipopeptides, but dispensable for TLR2 activation by triacylated lipopeptides. Indeed, synthetic MALP-2 containing an additional N-linked palmitoyl chain can activate TLR2 in the absence of TLR6 [49].

For many of these ligand–receptor interactions that involve well-defined lipids, there is no information on their effect on the adaptive immune responses in terms of polarization towards Th1, Th2 or Treg responses. A few studies involving complex antigen mixtures have shown that in mice deficient for MyD88 — an adapter protein that is essential for most signaling of TLR molecules — Th1 responses are impaired, indicating that interaction of bacterial lipids with TLR molecules induces Th1 responses [50, 51]. However, a few reports have also indicated that several bacterial acyl-containing ligands for TLR2 can inhibit activation of cells of the innate immune system. The 19 kDa lipoprotein of *Mycobacterium tuberculosis* and *Treponema pallidum* lipopeptides inhibit MHCII expression and antigen-processing by macrophages [52]. Such down-regulation of events that are critical in activation of adaptive immune responses is expected to lead to immune hyporesponsiveness.

In addition to bacteria, intracellular protozoa harbor lipids that interact with the immune system. For example, GPI anchors of *T. cruzi* are able to activate TLR2. These GPI anchors can suppress immune responses by inhibiting maturation of human DC, as well as production of TNF- α , IL-10 and IL-12p40 in both DC and macrophages [53]. Activation of the innate immune system by *T. cruzi* GPI anchors is mainly mediated by the lipid moiety, which can be a glycerolipid or a ceramide. Particularly the presence of an unsaturated fatty acid at the sn-2 position potentiates TLR-2 activation [54] (Fig. 3). In the protozoan parasite *Leishmania major*, the major parasite surface molecule lipophosphoglycan also has immunomodulatory properties, as it inhibits the migration of Langerhans cells out of the skin to the lymph node [55]. This would be expected to curtail the immune response to the invading *Leishmania* parasite.

Recent studies involving helminth parasites have shown that these multicellular eukaryotes possess lipids with

immunomodulatory properties. When lipids from schistosomes were fractionated into different classes and their effects on DC were analyzed, it became clear that the fraction containing phosphatidylserines could interact with DC and affect their T cell polarizing capacity. Further purification of the active components revealed that di-acylated phosphatidylserine promotes maturation of DC into a phenotype (termed DC2) that induces development of Th2 responses, whereas mono-acylated lysophosphatidylserine (lyso-PS) acts on DC to promote development of Treg cells by inducing a so-called DCreg phenotype (Fig. 4). Interestingly, although lyso-PS contains only one acyl chain, the effect of this schistosomal lipid was mediated by TLR2 [19]. Since not all TLR2 ligands have the capacity to induce development of DCreg cells (van der Kleij, unpublished observations), additional receptors and/or accessory molecules are likely to cooperate with TLR2 to define the outcome of pathogen recognition. For details on interactions between signaling of TLR molecules and other receptors, the reader is referred to a recent mini-review in this journal [56].

TLR activation by lyso-PS appears to be a unique property of lyso-PS derived from schistosomes, as mammalian lyso-PS was found to be inactive [19]. Phosphatidylserines from schistosomes have acyl chains that are not commonly found in mammals; they contain long, unsaturated fatty acids that may well be important for biological activity. Schistosomes do not synthesize fatty acids *de novo* but rely on the host for fatty acid supply. Most lipids found in schistosomes have indeed been synthesized by the host on which they feed. However, the parasite has retained the capability to modify host-derived fatty acids by chain elongation, resulting in a fatty acid profile that is clearly distinctive from that of the host [57]. For example, 20:1 and 22:4 are fatty acids that are prominently present in schistosomes but have not been found in mammals [58, 59].

In addition to chain elongation, schistosomes are capable of modifying host fatty acids in another way, resulting in the presence of octadec-5-enoic acid (18:1 Δ 5). This unusual fatty acid was found to be exclusively present on the tegument of the schistosome and is absent from the host [60]. Schistosomes display a high rate of deacylation and reacylation, in contrast to host cells [61], thereby exposing the host cells to lysophospholipids (which are formed upon deacylation of phospholipids) and free fatty acids. In high concentrations, lysophospholipids and fatty acids have a general destabilizing effect on the host cell membranes and can induce cell lysis [62, 63], but are also active in low concentrations and modulate cells of the innate immune system [19].

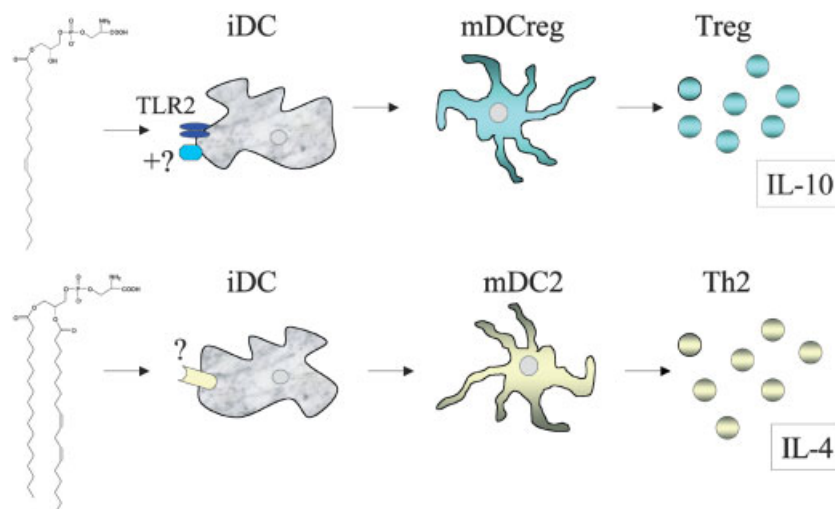


Fig. 4. Immune polarization by schistosomal phosphatidylserines. Schistosomal lyso-PS activates TLR2, which probably acts in concert with another, as-yet unidentified, receptor to polarize maturation of human immature DC (iDC) into a mature DC phenotype (mDCreg) that instructs naive T cells to polarize into Treg cells. These Treg cells are capable of suppressing proliferation of bystander T cells by producing IL-10. Schistosomal phosphatidylserine acts on an unknown receptor on iDC to induce maturation into a phenotype (mDC2) that polarizes the development of naive T cells into Th2 cells (which are characterized by the production of IL-4). Both lyso-PS and phosphatidylserine contain acyl moieties that are not commonly found in mammals.

Recent work on *Ascaris lumbricoides* has indicated that this intestinal helminth also contains lipids that stimulate TLR2 and induce the development of Th2 and Treg cells (van Riet, unpublished), but the structures involved have yet to be characterized.

In helminth lipids, immunomodulatory properties are not restricted to phosphatidylserines, but can also be found in glycolipid preparations. Glycolipids isolated from *Ascaris suum* stimulate the production of inflammatory cytokines in peripheral blood mononuclear cells. Within these structures, biological activity could be attributed to phosphocholine moieties that are covalently attached to the carbohydrate headgroup of the glycolipids [64]. In contrast to glycolipids from nematodes (such as *Ascaris*), glycolipids from schistosomes (which are trematodes) do not contain such phosphocholine-containing headgroups. Nevertheless, schistosomal glycolipids were found to induce production of pro- and anti-inflammatory cytokines in monocytes [65], and polarize DC maturation into a phenotype that promotes development of Treg cells and Th2 cells (van der Kleij et al., unpublished observations), indicating that for glycolipids of trematodes the presence of certain carbohydrates and/or lipid moieties is sufficient for biological activity, independently of a phosphocholine headgroup.

The fatty acid composition of *S. mansoni* glycosphingolipids is completely different from that of other lipids in this parasite. Whereas phospholipids, tri-acylglycerols

and free fatty acids are all dominated by 16:0, 18:0, 18:1, 18:2, 20:1, 20:4 and 22:4 acyl chains [66], many glycosphingolipids were shown to contain acyl chains such as 24:0, 24h:0, 25:0, 26:0, 26:1, 26h:0, 27:0 and 28h:0 [67]. Although the biological significance of these moieties has yet to be determined, it is possible that such unusually long fatty acid chains are particularly suitable for recognition by the mammalian innate immune system.

2.4 Other relevant phosphocholine immunomodulatory lipids

In addition to lipids originating from pathogens or induced by pathogens, many other lipid molecules with immunosuppressive activity exist. Some of these lipids are structurally related to ones that have already been discussed and may turn out to play a role in host-pathogen cross-talk and therefore will be discussed below.

An important class of immunomodulatory lipids belonging to the eicosanoids are the cyclopentenone prostaglandins (cyPG), which are characterized by the presence of a highly reactive electrophilic carbon atom in the unsaturated carbonyl group of the cyclopentane ring, and have clear anti-inflammatory effects. A potent cyPG is the PGD2 metabolite 15deoxy $\Delta^{12,14}$ PGJ₂ (15dPGJ₂) (Fig. 2), which inhibits macrophage activation and suppresses pro-inflammatory signaling pathways including NF- κ B, AP-1 and STAT molecules [68, 69]. Furthermore,

15dPGJ₂ was shown to promote apoptosis *in vitro* [70] and to inhibit the stimulatory capacity of DC by inhibiting maturation, expression of costimulatory molecules and cytokine production (IL-12 and IL-10) [28, 71]. It is thought that 15dPGJ₂ is a ligand for peroxisome proliferator-activated receptor γ (PPAR γ), a receptor that has been implicated in down-regulation of inflammation [72], but several studies have shown that PGD2 metabolites also have modulatory effects independent of this receptor [69, 71, 73]. The therapeutic potential of 15dPGJ₂ has been tested in several animal models; it was shown to ameliorate adjuvant-induced arthritis in rats [74] and collagen-induced arthritis in mice [75], and moreover was shown to attenuate clinical signs of disease in experimental autoimmune encephalomyelitis [76].

Although the immunomodulatory effect of lyso-PS has so far only been found in schistosomes, it is possible that various classes of pathogens express such bioactive lysophospholipids. Therefore it is important to consider what is known about bioactive lysophospholipids so far. Whereas mammalian lyso-PS has no activity [19], other endogenous mammalian lysophospholipids do have modulatory functions [77] (Fig. 5). Lysophospholipids can be active at low concentrations through activation of G-protein-coupled receptors. These receptors can be divided into two subgroups, consisting of the EDG1–8 receptors encoded by endothelial differentiation genes, and the closely related receptors GPR4, OGR1, TDAG8 and G2A. Their main ligands are sphingosine-1-

phosphate (S1P) (for EDG1, 3, 5, 6, and 8), lysophosphatidic acid (lyso-PA) (for EDG2, 4, and 7), sphingosylphosphorylcholine (SPC) (for OGR1), galactosylsphingosine (for TDAG8) and lysophosphatidylcholine (lyso-PC) (for G2A).

Recent findings demonstrate that lysophospholipids play a role in activation, function and trafficking of leukocytes [78]. With respect to immune polarization, endogenous lysophospholipids have been shown to be active; lyso-PA and S1P suppress IL-12 and enhance IL-10 production in human DC, and polarize their maturation so that development of Th2 cells is favored [79, 80]. In relation to this finding, it is interesting to note that in asthmatics, levels of lysophospholipids were found to be elevated upon antigen challenge [81]. It has been proposed that lyso-PA contributes to the pathology of asthma by inducing aberrant airway repair and remodeling [82]. In contrast to lyso-PA, lyso-PC affects DC maturation into a phenotype that stimulates the development of IFN- γ -producing T cells [83]. However, lyso-PC appears to have an important immune down-modulatory function as well: deletion of the murine gene encoding its receptor G2A, that is normally constitutively expressed on immune cells, resulted in adult-onset autoimmune disease similar to human systemic lupus erythematosus [84]. The discrepancy between these findings may indicate that other receptors are involved in recognition of lyso-PC, or that ligands other than lyso-PC act on the G2A receptor to induce immune suppression.

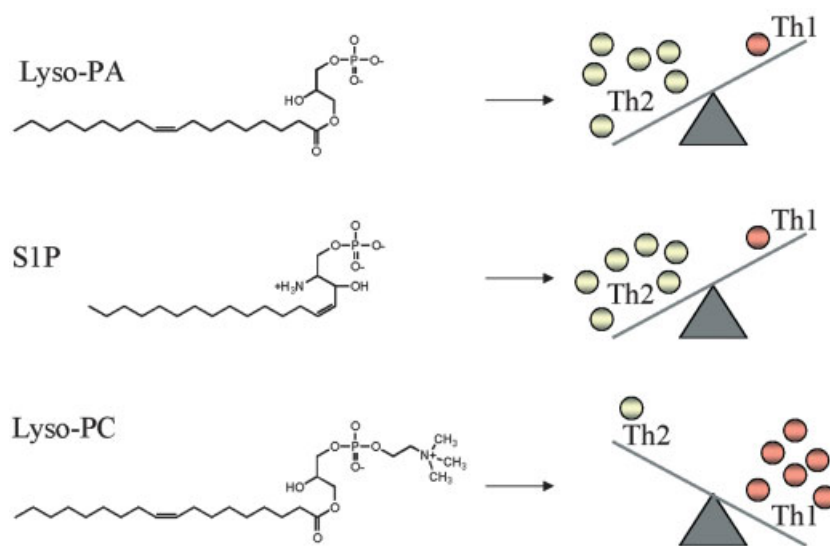


Fig. 5. Immune polarization by endogenous lysophospholipids. Lyso-PA and sphingosine-1-phosphate (S1P) polarize the development of the immune response towards Th2, whereas lyso-PC skews towards Th1.

It is striking that lyso-PA and lyso-PC — molecules that are structurally very similar (Fig. 5) — have such opposite effects on immune polarization. These findings imply that whereas the presence of one acyl chain is required for receptor ligation (di-acylated phospholipids are not active), the headgroup determines which receptor is bound and what type of immune response is induced. In addition, other co-receptors that may act in concert with the receptors described above could be involved in initiation of immune polarization.

A relationship between exposure of cells of the innate immune system to mammalian diacylated phosphatidylserine and the induction of an anti-inflammatory state was found in the process of apoptotic cell clearance. Within normal cells, the presence of phosphatidylserine is restricted to the inner leaflet of the cell membrane. In apoptotic cells, however, phosphatidylserine is exposed in the outer leaflet, where it can be recognized by macrophages via receptors mediating the engulfment of apoptotic cells, such as CD36 and the phosphatidylserine receptor (Fig. 1) [85, 86]. Ingestion of apoptotic cells by macrophages induces TGF- β 1 secretion, resulting in suppression of proinflammatory mediators [87].

In addition, the interaction of DC with apoptotic cells has been shown to inhibit maturation, resulting in DC that express low levels of MHC and secrete high levels of IL-10 [88, 89]. These cells are thought to induce tolerance by inducing the development of Treg cells [90]. This pathway may be exploited by helminths in two ways. First, it has been found that *Brugia malayi* microfilariae induce apoptosis in host cells [91, 92], and this in turn may induce development of Treg cells and immune hyporesponsiveness as discussed above. Second, given that schistosomal lyso-PS also induces Treg cell development, it is tempting to suggest that schistosomes exploit the mechanism normally used by their host to prevent excessive inflammation and autoimmune reactions in response to apoptosis.

3 Final remarks

Taken together, lipids form a class of molecules with a wide variety of potent immunomodulatory effects. Pathogens have evolved to live and reproduce effectively within their mammalian host, and in order to do so appear to express a diverse array of molecules that have immune suppressive effects. Many of these molecules are lipids or are lipidated in nature. The exposure of the immune system to these molecules, either as a result of the presence of a pathogen or exposure to pathogen-derived molecules in the environment, may promote the development of immune responses that have evolved

with a high burden of pathogens. This pathogen-educated immune system would have a robust anti-inflammatory network that may keep excess inflammatory responses under control. By identifying such molecules and their receptors we may be able to develop new therapeutics to combat diseases such as asthma and autoimmunities when inappropriate inflammatory responses cause organ pathology.

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