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REVIEW ARTICLE

Adjuvants that Enhance Th2 or Tr Responses

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ABSTRACT

It is well-known that many isoforms of toll-like receptors (TLRs) function as Th1 adjuvant receptors. Thus, the ligands induce Th1 differentiation in an antigen non-specific manner. During the past few years, not only Th1, but also Th2 adjuvants have been reported. Allergy-inducing materials, such as parasites, first stimulate dendritic cells (DCs) to change their character as professional antigen-presenting cells. Such a DC population (DC2) can stimulate naive CD4T cells to induce differentiation into Th2. In some instances, DCs that can stimulate regulatory T cells are also induced. Interestingly, many of such substances are glycolipids or phospholipids that mammalian species do not usually carry. In this paper, we show a cellular and molecular basis for Th2 adjuvants.

KEY WORDS

adjuvants, allergy, dendritic cells, HLA, Notch ligands, Th2, toll-like receptors

INTRODUCTION

Recent progress in dendritic cell (DC) research revealed that DCs with a specific character play pivotal roles in inducing Th2 responses. Moreover, allergy-inducing substances, carry not only protein allergen but also other biological activities that relate to allergy. Most of these activities are carried by small molecules with adjuvant properties. DCs are usually located in the interface between such environment and the human body. In this sense, DCs play distinct roles, compared with T cells and B cells. Thus, adjuvant activities affect DCs to exert allergen non-specific induction of allergic responses.

TH1 ADJUVANTS

Toll-like receptor (TLR) molecules expressed on DCs function as adjuvant receptors.[1] Environmental molecules, such as certain nucleic acids,[2,3] lipopolysaccharides (LPS),[4] and fungus-derived glycoprotein molecules,[5] alter DC function, by binding with a certain isoform of TLR, and they usually induce Th1 responses. Because such DCs induce Th1 responses, they are designated DC1, and such environmental molecules are called Th1 adjuvants (Fig. 1).

TH2 ADJUVANTS

DC2 and Th2 adjuvants have been recently reported. Th2 adjuvants induce Th2 responses in an antigen non-specific manner, through the induction of DC2. In other words, DCs that stimulate Th2 differentiation are called DC2. Whelan *et al.* reported in 2000 the Th2 adjuvant ES-62.[6] ES-62 is a phosphorylcholine-containing glycoprotein derived from nematode of filaria. Bone marrow-derived immature DCs were first incubated with GM-CSF and ES-62 for 24 hours, followed by co-incubation with naive CD4T cells of DO11.10-Tg mice, in the presence of OVA peptide. Activated T cells were then re-stimulated with PMA + ionomycin, and their cytokine production levels were determined. Indeed, ES-62 apparently increased the IL-4/IFN-γ ratio, without affecting CD80/86 balance.

van der Kleij *et al.* reported in 2002 that schistosoma-derived phosphatidylserine directly stimulates DCs and leads to Th2 induction (Fig. 2). Interestingly, neither synthetic nor mammalian phosphatidylserine has such an activity. Schistosoma-derived phosphatidylserine supposedly exhibits such an activity through a unique structure in its acyl base.[7] In other words, parasites carry "allergens", because they also carry Th2 adjuvant activity in an antigen non-specific manner.

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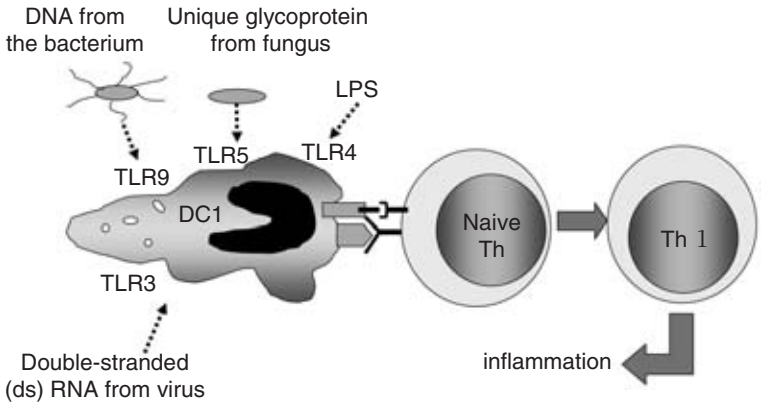

Fig. 1 Th1 adjuvant. DCs stimulated with pathogen-associated molecular patterns (PAMPs) derived from microbes induce differentiation of naive T cells into Th1 cells. TLR3, TLR7, TLR8 and TLR9 exist in the endosomes, while the other TLR isoforms are expressed on the plasma membrane.

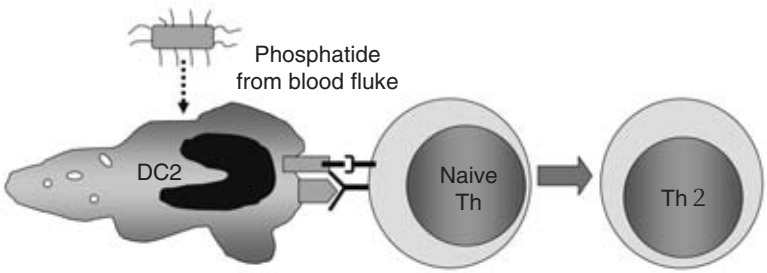

Fig. 2 Th2 adjuvant. DCs stimulated with phospholipids derived from helminth induce differentiation of naive T cells into Th2 cells.

Schistosomas do not synthesize fatty acids *de novo*. They modify the structure of host-derived fatty acids, by using their own enzymes to elongate the acyl base, thus allowing the appearance of parasite-specific fatty acids, in the host-parasite interface. Interestingly, unsaturated lysophosphatidylserine (lyso-PS) with a single acyl base, tends to modify DC function to induce IL-10-producing regulatory T cells (Tr). This is partially blocked by a neutralizing antibody to TLR2. On the other hand, Th2-inducing phosphatidylserine with two acyl bases does not appear to use TLR2 (Fig. 3).[8,9] Lysophosphatidic acid (Lyso-PA) and sphingosine-1-phosphate (S1P) also induce DC2, whereas lysophosphatidylcholine (Lyso-PC) induces DC1. Because they are structurally similar in their acyl bases, head groups might be important in determining their activity (Fig. 4).

It is yet to be determined as to what molecules on DCs regulate T-cell differentiation. CCL2 or monocyte chemoattractant protein-1 (MCP-1) are produced by DCs. Gu *et al.* reported that in CCL2-/- mice, decreased levels of Th2 and IgG1 responses to TNP-OVA are observed. Indeed, they become resistant to leishmania infection.[10] However, CCL2 activity in humans has not yet been delineated. Certain immunity-related molecules such as thymic stromal lymphopoietin (TSLP) are differentially expressed between humans and mice, raising the possibility that rules in mice do not apply to humans.

Prostaglandins (PG), especially, PGE2 and PGD2 have been reported to carry Th2 adjuvant activity. In this concern, Kalinski *et al.* reported that immature DCs produce IL-12p40, when stimulated with TNF-α and PGE2. Indeed, monomeric or homodimeric p40 act as antagonists for IL-12p70, allowing PGE2 to function as a Th2 adjuvant. However, this is not the only one mechanism by which PGE2 functions as a Th2 adjuvant. Other mechanisms include: 1) PGE2 acts directly on T cells and suppress IFN-γ production; 2) PGE2 inhibits IL-12R expression; and 3) PGE 2 stimulates monocytes to produce IL-10.[11] Another topic in this concern is a recent observation that pollen carries molecules cross-reactive with human PGE 2 or leukotriens.[12]

Other Th2 adjuvants include molecules expressed by *C. albicans*, histamine, G protein-R, PRR glycolipids, OX40L, Jagged 1, and Pam3Cys-Ser-Lys4 (Pam3Cys). Pam3Cys is an active moiety of

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