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 [Volume 94](#)

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DNA immunization circumvents deficient induction of T helper type 1 and cytotoxic T lymphocyte responses in neonates and during early life.

[Martinez X](#), [Brandt C](#), [Saddallah F](#), [Toungne C](#), [Barrios C](#), [Wild F](#), [Dougan G](#), [Lambert PH](#), [Siegrist CA](#)

Proc Natl Acad Sci U S A 1997 Aug 5 **94:16** 8726-31

Abstract

The relative deficiency of T helper type 1 (Th1) and cytotoxic T lymphocyte (CTL) responses in early life is associated with an increased susceptibility to infections by intracellular microorganisms. This is likely to reflect a preferential polarization of immature CD4 T cells toward a Th2 rather than a Th1 pattern upon immunization with conventional vaccines. In this report, it is shown that a single immunization within the first week of life with DNA plasmids encoding viral (measles virus hemagglutinin, Sendai virus nucleoprotein) or bacterial (C fragment of tetanus toxin) vaccine antigens can induce adult-like Th1 or mixed Th1/Th2 responses indicated by production of IgG2a vaccine-specific antibodies and preferential secretion of interferon-gamma (IFN-gamma) compared with interleukin (IL)-5 by antigen-specific T cells, as well as significant CTL responses. However, in spite of this potent Th1-driving capacity, subsequent DNA immunization was not capable of reverting the Th2-biased responses induced after early priming with a recombinant measles canarypox vector. Thus, DNA vaccination represents a novel strategy capable of inducing Th1 or mixed Th1/Th2 and CTL responses in neonates and early life, providing it is performed prior to exposure to Th2-driving conventional vaccine antigens.


MeSH

[Animal](#) ; [Animals, Newborn](#) ; [Antigens, Viral](#) ; [Immunity, Natural](#) ; [Immunization](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Mice, Inbred C57BL](#) ; [Support, Non-U.S. Gov't](#) ; [T-Lymphocytes, Cytotoxic](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Vaccines, DNA](#) ; [Virus Diseases](#) ;

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The TH1/TH2 paradigm in allergy.

[Maggi E](#)

Immunotechnology 1998 Jan **3:4** 233-44

Abstract

Recent evidence has been accumulated to suggest that allergen-reactive type 2 helper T cells (Th2) play a triggering role in the activation and/or recruitment of IgE antibody-producing B cells, mast cells and eosinophils, i.e. the cellular triad involved in the allergic inflammation. Interleukin (IL)-4 production by a still unknown cell type (T cell subset, mast cell/basophil?) at the time of antigen presentation to the Th cell is critical for the development of Th2 cells. Other

cytokines, such as IL-1 and IL-10, and hormones, such as calcitriol and progesterone, also play a favoring role. In contrast, cytokines such as interferon (IFN-alpha, IFN-gamma, IL-12 and transforming growth factor (TGF)-beta, and hormones, play a negative regulatory role on the development of Th2 cells. However, the mechanisms underlying the preferential activation by environmental allergens of Th2 cells in atopic individuals still remain obscure. Some gene products selectively expressed in Th2 cells or selectively controlling the expression of IL-4 have recently been described. Moreover, cytokines and other gene products that dampen the production of IL-4, as well as the development and/or the function of Th2 cells, have been identified. These findings allow us to suggest that the up-regulation of genes controlling IL-4 expression and/or abnormalities of regulatory mechanisms of Th2 development and/or function may be responsible for Th2 responses against common environmental allergens in atopic people. The new insights in the pathophysiology of T cell responses in atopic diseases provide exciting opportunities for the development of novel immunotherapeutic strategies. They include the induction of nonresponsiveness in allergen-specific Th2 cells by allergen peptides or redirection of allergen-specific Th2 responses by Th1-inducing cytokines, altered peptide ligands, allergens incorporated into recombinant microorganisms or bound to appropriate adjuvants, and plasmid DNA vaccination. In severe atopic patients, the possibility of nonallergen-specific immunotherapeutic regimens designed to target Th2 cells or Th2-dependent effector molecules, such as specific IL-4 transcription factors, IL-4, IL-5 and IgE, may also be suggested.

MeSH

[Animal](#) ; [Cytokines](#) ; [Human](#) ; [Hypersensitivity](#) ; [Immunotherapy](#) ; [Lymphocyte Transformation](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ;

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[Diabetologia](#)

[Volume 39](#)

[Issue 12](#)

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Cytokine gene expression in the BB rat pancreas: natural course and impact of bacterial vaccines.

[Kolb H](#), [Wörz-Pagenstert U](#), [Kleemann R](#), [Rothe H](#), [Rowell P](#), [Scott FW](#)

Diabetologia 1996 Dec **39**:12 1448-54

Abstract

In diabetes prone BB rat pancreas the Th1/ Th2 cytokine balance and the expression of inducible nitric oxide synthase (iNOS) was determined by mRNA analysis before and after the onset of insulinitis. Specific mRNA was amplified by reverse transcriptase polymerase chain reaction, quantitated with radiolabelled probes by phosphoimaging and calibrated with the amount of co-amplified beta-actin mRNA. At 50 days of age, prior to recognizable insulinitis, there was already significantly enhanced expression of both, Th1 and Th2 cytokines, and of iNOS mRNA, when compared to Wistar rat pancreas ($p < 0.001$). This supports the concept of an inconspicuous early phase of islet infiltration by single immunocytes, called single cell insulinitis. At 70 days of age mononuclear infiltration of islets had begun and was associated with upregulation of interferon gamma (IFN gamma) and iNOS, but downregulation of interleukin-10 and transforming growth factor beta mRNA ($p < 0.001$). These findings correlate the onset of insulinitis with a shift of the Th1/Th2 cytokine balance towards Th1 cell reactivity. Indeed there was a close correlation of the Th1/Th2 cytokine ratio but not of absolute IFN gamma mRNA levels with the insulinitis score. Vaccination at day 50 with tetanus toxoid did not affect cytokine gene expression while diphtheria toxoid and even more strongly BCG administration induced a shift towards Th2 reactivity ($p < 0.001$) while iNOS mRNA was decreased ($p < 0.01$). Oral dosing with immunostimulatory components of *Escherichia coli* also changed the quality of inflammation. Oral lipopolysaccharide (LPS) from *E. coli* and OM-89, an endotoxin free extract containing immunostimulatory glycolipopeptides and heat shock protein (hsp) 65, both downregulated IFN gamma mRNA while only OM-89 in addition suppressed iNOS mRNA and enhanced Th2 cytokine gene expression ($p < 0.001$). We conclude that the onset of insulinitis is associated with a shift towards Th1 cytokine and iNOS gene expression. Diphtheria toxoid and BCG vaccination stimulates Th2 reactivity but does not downregulate Th1. The latter can be achieved through oral administration of LPS or a glycopeptide fraction (OM-89) from *E. coli*.


MeSH

[Administration, Oral](#) ; [Animal](#) ; [Bacterial Vaccines](#) ; [Comparative Study](#) ; [Cytokines](#) ; [Diabetes Mellitus, Insulin-Dependent](#) ; [Diphtheria Toxoid](#) ; [Disease Models, Animal](#) ; [Escherichia coli](#) ; [Gene Expression Regulation](#) ; [Interferon Type II](#) ; [Interleukin-10](#) ; [Lipopolysaccharides](#) ; [Mycobacterium bovis](#) ; [Nitric-Oxide Synthase](#) ; [Pancreas](#) ; [Random Allocation](#) ; [Rats](#) ; [Rats, Inbred BB](#) ; [Rats, Wistar](#) ; [Regression Analysis](#) ; [RNA, Messenger](#) ; [Specific Pathogen-Free Organisms](#) ; [Support, Non-U.S. Gov't](#) ; [Tetanus Toxoid](#) ; [Transforming Growth Factor beta](#) ;

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 [J Theor Biol](#)

 [Volume 170](#)

[Issue 1](#)

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Th1/Th2 cross regulation.

[Fishman MA, Perelson AS](#)

J Theor Biol 1994 Sep 7 **170**:1 25-56

Abstract

We present and analyze a model for the cross-regulation of the Th1 and Th2 helper cell subsets during an immune response by the regulatory cytokines interferon-gamma (IFN-gamma) and interleukin-10 (IL-10). IFN-gamma, secreted by Th1 cells, can inhibit the proliferation of Th2 cells. Interleukin-10, secreted by Th2 cells, inhibits cytokine production by Th1 cells. Based on these properties, the model shows that responses are expected to be dominated by either Th1 cells or Th2 cells but not both. Which type dominates is shown to depend principally on the relative efficiencies of activation of the responding Th1 and Th2 cells. However, our model, as well as numerous experiments, show that perturbations of the system allow one to switch from a Th2 to a Th1 response, or vice versa. Our model can account for observed outcomes of parasitic infection and may also contribute to our understanding of immune responses to HIV infection as well as to tolerance to self components. It also predicts that in certain parameter ranges vaccination with low doses of live parasites can provide protection against subsequent encounters with high doses that normally induce disease. Experiments by Bretscher et al. (1992, *Science* 257, 539) on *Leishmania* major infection are consistent with this prediction. A similar strategy may also be relevant for the design of an AIDS vaccine. Lastly, our results indicate that Th1/Th2 cross-regulation is capable of generating a "sneaking through" phenomenon, and hence it may play a role in tumor immunity.


MeSH

[Animal](#) ; [Antibody Formation](#) ; [Immunity, Cellular](#) ; [Interferon Type II](#) ; [Interleukin-10](#) ; [Lymphocyte Cooperation](#) ; [Lymphocyte Transformation](#) ; [Models, Biological](#) ; [Support, Non-U.S. Gov't](#) ; [Support, U.S. Gov't, Non-P.H.S.](#) ; [Support, U.S. Gov't, P.H.S.](#) ; [T-Lymphocyte Subsets](#) ; [T-Lymphocytes, Helper-Inducer](#) ;

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Zinc-controlled Th1/Th2 switch significantly determines development of diseases.

[Sprietsma JE](#)

Med Hypotheses 1997 Jul **49**:1 1-14

Abstract


Functional, excessive-possibly temporary-deficiencies of the trace element zinc can change immune functions prematurely from predominantly cellular Th1 responses to humoral Th2 responses. T helper (Th1) cells produce cytokines such as interleukin-2 (IL-2) and interferon gamma, thereby controlling viral infections and other intracellular pathogens more effectively than Th2 responses through cytokines such as IL-4, IL-5, IL-6 and IL-10. The accelerated shift from the production of extra Th1 cells during these cellular immune activities to more Th2 cells with their predominantly humoral immune functions, caused by such a zinc deficiency, adversely influences the course of diseases such as leprosy, schistosomiasis, leishmaniasis and AIDS, and can result in allergies. It is noteworthy that AIDS viruses (HIVs) do not replicate in Th1 cells, which probably contain more zinc, but preferentially in the Th0 and Th2 cells; all the more so, because zinc and copper ions are known to inhibit intracellular HIV replication. Considering the above Th1/Th2 switch, real prospects seem to be offered of vaccination against such parasites as *Leishmania* and

against HIVs.

MeSH

[Acquired Immunodeficiency Syndrome](#) ; [Animal](#) ; [Apoptosis](#) ; [Cytokines](#) ; [Human](#) ; [Hypersensitivity, Immediate](#) ; [HIV](#) ; [Leishmania](#) ; [Liver](#) ; [Mast Cells](#) ; [Mice](#) ; [Models, Biological](#) ; [Murine Acquired Immunodeficiency Syndrome](#) ; [Thymic Factor, Circulating](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Vaccination](#) ; [Virus Replication](#) ; [Zinc](#) ;



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Zinc-controlled Th1/Th2 switch significantly determines development of diseases. [Sprietsma JE](#)

Med Hypotheses 1997 Jul **49**:1 1-14

Abstract

Functional, excessive-possibly temporary-deficiencies of the trace element zinc can change immune functions prematurely from predominantly cellular Th1 responses to humoral Th2 responses. T helper (Th1) cells produce cytokines such as interleukin-2 (IL-2) and interferon gamma, thereby controlling viral infections and other intracellular pathogens more effectively than Th2 responses through cytokines such as IL-4, IL-5, IL-6 and IL-10. The accelerated shift from the production of extra Th1 cells during these cellular immune activities to more Th2 cells with their predominantly humoral immune functions, caused by such a zinc deficiency, adversely influences the course of diseases such as leprosy, schistosomiasis, leishmaniasis and AIDS, and can result in allergies. It is noteworthy that AIDS viruses (HIVs) do not replicate in Th1 cells, which probably contain more zinc, but preferentially in the Th0 and Th2 cells; all the more so, because zinc and copper ions are known to inhibit intracellular HIV replication. Considering the above Th1/Th2 switch, real prospects seem to be offered of vaccination against such parasites as Leishmania and against HIVs.

MeSH

[Acquired Immunodeficiency Syndrome](#) ; [Animal](#) ; [Apoptosis](#) ; [Cytokines](#) ; [Human](#) ; [Hypersensitivity, Immediate](#) ; [HIV](#) ; [Leishmania](#) ; [Liver](#) ; [Mast Cells](#) ; [Mice](#) ; [Models, Biological](#) ; [Murine Acquired Immunodeficiency Syndrome](#) ; [Thymic Factor, Circulating](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Vaccination](#) ; [Virus Replication](#) ; [Zinc](#) ;



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 [J Virol](#)

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Preferential recognition of hepatitis B nucleocapsid antigens by Th1 or Th2 cells is epitope and major histocompatibility complex dependent.

[Milich DR](#), [Peterson DL](#), [Schödel F](#), [Jones JE](#), [Hughes JL](#)

J Virol 1995 May **69**:5 2776-85

Abstract

Regulatory T-helper (Th) cells have been categorized into two functional subsets, Th1 and Th2 cells, which produce distinct lymphokines. In general, Th1 cells mediate cellular immune responses and Th2 cells mediate humoral immunity. Recent serological studies suggest that the Th1-Th2 balance may be relevant in acute and chronic hepatitis B virus (HBV) infections. The purpose of this study was to determine the potential of the nucleocapsid antigens (Ags) (hepatitis B core and e Ags [HBc/eAg]) of HBV to preferentially elicit either a Th1 or a Th2 dominant response. For this purpose, H-2 congenic B10.S and B10 mice were immunized with HBc/eAg, and Ag-specific T-cell proliferative responses, T-cell helper function, and T-cell cytokine production were analyzed. The results indicated that B10.S mice preferentially develop a Th1-like response whereas B10 mice preferentially develop a Th2-like response after immunization with HBc/eAg. Furthermore, the preferential Th1 and Th2 response patterns were reproduced when 12-residue peptides representing the dominant HBc/eAg-specific T-cell sites for B10.S (peptide 120-131) and B10 (peptide 129-140) mice were used as immunogens. Therefore, the combination of the T-cell site recognized and the

major histocompatibility complex restricting element can in large part determine the Th phenotype of the HBc/eAg-specific T-cell response. Other factors that influenced Th phenotype were the presence of exogenous cytokines, Ag structure, and tissue distribution.

MeSH

[Amino Acid Sequence](#) ; [Animal](#) ; [Cytokines](#) ; [Epitopes](#) ; [H-2 Antigens](#) ; [Hepatitis B e Antigens](#) ; [Hepatitis B Antigens](#) ; [Hepatitis B Core Antigens](#) ; [Hepatitis B Virus](#) ; [Lymph Nodes](#) ; [Lymphocyte Transformation](#) ; [Major Histocompatibility Complex](#) ; [Mice](#) ; [Mice, Inbred C57BL](#) ; [Mice, Transgenic](#) ; [Molecular Sequence Data](#) ; [Peptide Fragments](#) ; [Spleen](#) ; [Support, Non-U.S. Gov't](#) ; [Support, U.S. Gov't, P.H.S.](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ;

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Resistance of naive mice to murine hepatitis virus strain 3 requires development of a Th1, but not a Th2, response, whereas pre-existing antibody partially protects against primary infection.

[Pope M](#), [Chung SW](#), [Mosmann T](#), [Leibowitz JL](#), [Gorczyński RM](#), [Levy GA](#)

J Immunol 1996 May 1 **156**:9 3342-9

Abstract

Murine hepatitis virus strain 3 (MHV-3) produces a strain-dependent spectrum of disease. The development of liver necrosis has been shown to be related to production of a unique macrophage procoagulant activity (PCA), encoded by the gene *fgl-2*, in susceptible mice. These studies were designed to examine the influence of Th1/Th2 cells on resistance/susceptibility and production of macrophage PCA in resistant (A/J) and susceptible (BALB/cJ) strains of mice following infection with MHV-3. Immunization of A/J mice with MHV-3 induced a Th1 cellular immune response, and one Th1 cell line (3E9.1) protected susceptible mice and inhibited PCA production by macrophages both in vitro and in vivo. In contrast, immunization of BALB/cJ mice with an attenuated variant of MHV-3 derived from passaging MHV-3 in YAC-1 cells resulted in a Th2 response. Transfer of spleen cells and T cell lines from immunized BALB/cJ mice failed to protect naive susceptible syngeneic mice from infection with MHV-3 and augmented macrophage PCA production to MHV-3 in vitro. However, serum from immunized BALB/cJ mice contained high titrated neutralizing Ab that protected naive BALB/cJ animals from lethal primary MHV-3 infection. These results demonstrate that susceptible BALB/cJ mice generate a Th2 response following MHV-3 infection and that these Th2 cells neither inhibit MHV-3-induced macrophage PCA production nor protect naive mice from MHV-3 infection. The results suggest that Ab protects against primary infection but cannot eradicate ongoing infection. Thus, these data define the differential role of Th1/Th2 lymphocytes in primary and secondary MHV-3 infection and emphasize the importance of PCA in the pathogenesis of MHV-3 infection.

MeSH

[Animal](#) ; [Antibodies, Viral](#) ; [Blood Coagulation Factors](#) ; [Cell Line](#) ; [Coronavirus Infections](#) ; [Disease Susceptibility](#) ; [Female](#) ; [Gastroenteritis Virus, Murine](#) ; [Hepatitis, Viral, Animal](#) ; [Immunity, Natural](#) ; [Immunization, Passive](#) ; [Immunotherapy, Adoptive](#) ; [Macrophages](#) ; [Mice](#) ; [Mice, Inbred A](#) ; [Mice, Inbred BALB C](#) ; [Mice, Inbred C57BL](#) ; [Spleen](#) ; [Support, Non-U.S. Gov't](#) ; [Support, U.S. Gov't, P.H.S.](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Viral Vaccines](#) ;

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[Issue 2](#)

T-helper type-1-dominated lymph node responses induced in C57BL/6 mice by optimally irradiated cercariae of *Schistosoma mansoni* are down-regulated after challenge infection.

[Pemberton RM](#), [Wilson RA](#)

Immunology 1995 Feb **84**:2 310-6

Abstract

Following a single percutaneous vaccination with optimally irradiated cercariae of *Schistosoma mansoni*, C57BL/6 mice mount a T-helper type-1 (Th1) lymphocyte-dominant immune response and are highly resistant to challenge infection. In this study, we show that, besides interferon-gamma (IFN-gamma), lymph node (LN) cells draining the site of vaccination produce significant amounts of interleukin (IL)-4 and IL-10 in culture with parasite antigen. After a challenge infection at the original site of vaccination, these LN cells did not generate an anamnestic Th1 response. Paradoxically, IFN-gamma production and cell proliferation were profoundly down-regulated, whereas IL-4 production was enhanced and occurred earlier than in challenge control cultures. When challenge was applied to a site remote from vaccination, IFN-gamma down-regulation was less evident, but the IL-4 response was consistently enhanced. Neutralization of IL-10 in vitro restored IFN-gamma production by LN cells, whilst IL-4 levels were reduced. These data indicate that down-regulation of IFN-gamma is controlled by IL-10 and/or IL-4. Mice showing down-regulated Th1 responses in the LN after *S. mansoni* challenge infection did not have a reduced ability to eliminate challenge parasites, indicating that the post-vaccination Th1 response had already armed the lungs with effector T cells before administration of challenge parasites. The observed phenomena of down-regulated Th1 and enhanced Th2 responses may be of relevance to other systems involving multiple infections or vaccination/boosting. Repeated applications to percutaneous sites having common lymphatic drainage would be expected to favour Th2 responses. Alternatively, in order to induce Th1-dominant responses and avoid unwanted IL-4/IL-10 induction, the use of remote sites is indicated.

MeSH

[Animal](#) ; [Antigens, Helminth](#) ; [Cell Division](#) ; [Cells, Cultured](#) ; [Cytokines](#) ; [Female](#) ; [Immunization](#) ; [Interferon Type II](#) ; [Interleukin-10](#) ; [Interleukin-2](#) ; [Interleukin-4](#) ; [Lymph Nodes](#) ; [Mice](#) ; [Mice, Inbred C57BL](#) ; [Schistosoma mansoni](#) ; [Schistosomiasis mansoni](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ;

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Lack of Th1 or Th2 polarization of CD4+ T cell response induced by particulate antigen targeted to phagocytic cells.

[Sedlik C](#), [Dériaud E](#), [Leclerc C](#)

Int Immunol 1997 Jan **9**:1 91-103

Abstract

Several factors are involved in the selective activation of Th1 or Th2 subset of CD4+ T cells, such as the type of antigen-presenting cells, the dose of antigen, the route of immunization, etc. To analyze the influence of accessory cells on Th1/Th2 cell differentiation, we used a particulate antigen prepared by covalent linkage of hemocyanin (LH) to 1 microns synthetic microspheres. This particulate antigen was efficiently presented to T cells by macrophages but not by B lymphocytes. BALB/c mice immunized either with soluble LH in alum or with particulate LH without adjuvant produced both Th1 (IL-2 and IFN-gamma) and Th2 (IL-4 and IL-5) cytokines. Moreover, mice primed either with soluble or particulate LH secreted higher levels of IgG1- than of IgG2a-specific antibodies. The induction of this cytokine profile response was independent of the route of administration of the antigen, and was observed both in BALB/c and C57BL/6 mice. In contrast, immunization of mice with particulate LH in the presence of poly(I):(C) or of IL-12 induced a strong activation of Th1 cells, as shown by an up-regulated IFN-gamma production, and by decreased IL-4 and IL-5 levels associated to a greatly enhanced IgG2a antibody response. These results therefore demonstrate that targeting the antigen to phagocytic cells is not sufficient to stimulate a polarized Th response and that environmental cytokines play the major role in the selective activation of Th1 cells. This study provides important conclusions for the development of new vaccines and shows that particulate antigen associated with appropriate cofactor can selectively activate Th1 cells.


MeSH

[Animal](#) ; [Antigen Presentation](#) ; [Antigens](#) ; [Cell Polarity](#) ; [Cytokines](#) ; [CD4-Positive T-Lymphocytes](#) ; [Female](#) ; [Hemocyanin](#) ; [IgG](#) ; [Interleukin-12](#) ; [Lymphocyte Transformation](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Mice, Inbred C57BL](#) ; [Particle Size](#) ; [Phagocytes](#) ; [Poly I-C](#) ; [Solubility](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ;

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Analysis of a TH1----TH2 helper cell circuit.

[McNamara M](#), [Kang CY](#), [Kohler H](#)

J Immunol 1985 Sep **135**:3 1603-9


Abstract

In the present study, the T15 idiotype-recognizing T helper cell circuit was dissected with respect to its homeostasis, interactive specificity, stability over time, and effects on B cell expression. Analysis of the TH1 cells by adoptive transfer experiments indicates their short-lived state of activity, during which TH2 cells are stimulated. TH1 cell activity was also directly monitored by the use of TNP-anti-T15 hybridoma antigens. It was found that TH1 cells are detected 1 wk after priming with PC-Hy, whereas TH2 cells become activated after 4 wk of priming. Comparative analysis of TH1 cells by using two different TNP-anti-T15 hybridoma antigens indicates a TH1 specificity for a shared idiotope. The stability over time of the TH1----TH2 circuit was demonstrated by comparing TH2 frequencies in young and old mice. Finally, we addressed the question of the function of the idiotype-recognizing T helper cells and showed that stimulation of T15-idiotype-specific TH2 cells can be correlated with a significant increase in the percentage of T15 idiotype in an anti-PC response. Collectively, these data describe an idiotype-specific T helper circuit as part of the network homeostasis of the immune system.

MeSH

[Age Factors](#) ; [Animal](#) ; [Antibody Formation](#) ; [B-Lymphocytes](#) ; [Dose-Response Relationship, Immunologic](#) ; [Female](#) ; [Immunization, Passive](#) ; [Immunoglobulin Idiotypes](#) ; [Immunologic Memory](#) ; [Lymphocyte Cooperation](#) ; [Male](#) ; [Mice](#) ; [Phosphorylcholine](#) ; [Support, Non-U.S. Gov't](#) ; [Support, U.S. Gov't, P.H.S.](#) ; [T-Lymphocytes, Helper-Inducer](#) ; [Time Factors](#) ; [Trinitrobenzenes](#) ;



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Th1/Th2 cytokine responses following HIV-1 immunization in seronegative volunteers. The AIDS Vaccine Evaluation Group.

[Evans TG](#), [Fitzgerald T](#), [Gibbons DC](#), [Keefer MC](#), [Soucier H](#)

Clin Exp Immunol 1998 Feb **111**:2 243-50

Abstract

The Th1/Th2 profile that follows human vaccination may profoundly influence the subsequent course of disease after infection. However, the ability to detect IL-4 has been limited outside trials of live vaccination. By using methods in which memory effector cells are allowed to antigenically expand by short term culture, followed by low-dose mitogenic stimulation, we have been able to follow the Th1/Th2 profile in HIV-1 volunteers enrolled in two phase I studies of HIV immunogens (a recombinant gp120 and a multivalent, octameric V3 loop peptide). Antigen-specific interferon-gamma (IFN-gamma) could be detected in primary stimulation, but IL-4 was observed only after antigenic expansion and restimulation. In both of these studies the responses after initial immunizations were dominated by IFN-gamma, with IL-4 appearing only after multiple rounds of immunization, and IL-4 was temporally related to

antibody production. Concomitant with the IL-4 production, the amount of supernatant IFN-gamma declined. Antigen-specific IL-10 was not detected in either study. Such techniques, which have been shown to correlate with outcomes in immunotherapy, may prove useful as future surrogates of human vaccine response.

MeSH

[AIDS Vaccines](#) ; [Cells, Cultured](#) ; [Culture Media](#) ; [Cytokines](#) ; [Human](#) ; [HIV Envelope Protein gp120](#) ; [Influenza Vaccine](#) ; [Lymphocyte Transformation](#) ; [Phenotype](#) ; [Support, U.S. Gov't, P.H.S.](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Vaccination](#) ;

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[Volume 160](#)

[Issue 8](#)

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Induction of a Th1 immune response and simultaneous lack of activation of a Th2 response are required for generation of immunity to leishmaniasis.

[Sjölander A](#), [Baldwin TM](#), [Curtis JM](#), [Handman E](#)

J Immunol 1998 Apr 15 **160**:8 3949-57

Abstract

Experimental systems based on immunization with plasmid DNA or immune-stimulating complexes were used to delineate the requirements for generation of protective immunity against murine leishmaniasis. Vaccination with plasmid DNA encoding the host-protective *Leishmania* major parasite surface Ag-2 primed for an essentially exclusive Th1 response that protected mice against *L. major* infection. In contrast, parasite surface Ag-2 in immune-stimulating complexes generated an immune response with mixed Th1-like and Th2-like properties that was not protective despite the activation of large numbers of CD4+ T cells secreting IFN-gamma. These results indicate that a Th1 response is sufficient to protect against cutaneous leishmaniasis, but the induction of a simultaneous Th2 response abrogates the Th1 effector function. DNA vaccines may therefore have an advantage for diseases in which protection depends on the induction of Th1 responses.

MeSH

[Animal](#) ; [Antibodies, Protozoan](#) ; [Antigens, Protozoan](#) ; [Antigens, Surface](#) ; [Cytokines](#) ; [CD4-Positive T-Lymphocytes](#) ; [DNA, Protozoan](#) ; [Female](#) ; [IgG](#) ; [ISCOMs](#) ; [Leishmania major](#) ; [Leishmaniasis, Cutaneous](#) ; [Lymphocyte Transformation](#) ; [Mice](#) ; [Mice, Inbred C3H](#) ; [Spleen](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Vaccination](#) ; [Vaccines, DNA](#) ;

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[J Theor Biol](#)

[Volume 190](#)

[Issue 2](#)

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On the role of a possible dialogue between cytokine and TCR-presentation mechanisms in the regulation of autoimmune disease.

[Bar-Or RL](#), [Segel LA](#)

J Theor Biol 1998 Jan 21 **190**:2 161-78

Abstract

Autoimmune diseases are thought to occur through some weakness in an active process of autoregulation. Two different regulatory mechanisms have been proposed separately during the years: a "non-specific" mechanism, via

Th1-Th2 non-specific cytokines, and a "specific" one-on-one mechanism, via presentation of peptides, i.e., T cell receptor (TCR) peptides, by the T cells themselves. Several anti-idiotypic models rely on the latter to explain the effects of "T-cell-vaccination" therapy. We present and analyse a model for the interaction between both regulatory mechanisms within an ensemble composed of Th1 and Th2 cells. Our model shows how both TCR presentation and non-specific Th1/2 signals can cooperate in the choice of the prevailing Th1 or Th2 response. We show how TCR presentation can foster regulation, without necessitating a particular "suppressor" agent, of the type that some have assumed to play a central role in the regulation of autoimmunity. Our results suggest an important role for the cells' sensitivities to Th1 and Th2 derived cytokines; only for certain sensitivity ranges, is it possible to switch dominance between subtypes. It is argued that memory is sustained via modulation of sensitivities to cytokines, not only to antigens. The results and hypotheses also suggest one possible reason for the known correlation between standard and autoimmune diseases. Several therapies and informative experiments are suggested. We argue, for example, that administering a non-relevant peptide while increasing the ratio between the clones reactive to it and other clones in the pancreas, might cure autoimmune diabetes. Moreover, we predict that disease could be prevented by administering an autoimmune peptide at an early age while forcing the system to react in a Th2 fashion.

MeSH

[Antigen-Presenting Cells](#) ; [Autoimmune Diseases](#) ; [Cytokines](#) ; [Homeostasis](#) ; [Human](#) ; [Models, Immunological](#) ; [Receptors, Lymphocyte Homing](#) ; [Support, Non-U.S. Gov't](#) ; [Support, U.S. Gov't, Non-P.H.S.](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ;

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 [Cell Immunol](#)

 [Volume 170](#)

[Issue 1](#)

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Dendritic cells in antitumor immune responses. II. Dendritic cells grown from bone marrow precursors, but not mature DC from tumor-bearing mice, are effective antigen carriers in the therapy of established tumors.

[Gabrilovich DI](#), [Nadaf S](#), [Corak J](#), [Berzofsky JA](#), [Carbone DP](#)

Cell Immunol 1996 May 25 **170**:1 111-9

Abstract

Antitumor CTL responses were studied in a model tumor hearing a mutant human p53 gene. We found ineffective induction of antitumor CTL in mice bearing these tumors associated with measurable defects in the function of dendritic cells (DC) from these animals. In this study we investigate the mechanism of this defect in mature DC and find that functional DC can be generated by growth from the bone marrow of tumor-bearing animals. Tumor cell supernatants did not affect the function of mature DC obtained from the spleen of tumor-bearing animals, but significantly suppressed the ability to generate functional DC from the bone marrow of control mice in vitro. This suggests that tumor cells may release factors which block early stages of DC maturation from precursors. DC generated from the bone marrow of tumor-bearing mice showed normal potential to stimulate allogeneic T cells, to stimulate anti-mutant p53 peptide-specific cytotoxic T cells, and to induce anti-p53 CTL responses in vivo in control mice. Repeated immunization with peptide-pulsed DC generated from the bone marrow of control mice (every 4-5 days) blocked progression of established tumors. Immunization of mice with peptide-pulsed DC obtained from the spleen of tumor-bearing mice (4 weeks after tumor injection) did not affect the tumor growth, whereas immunization with peptide-pulsed DC generated from bone marrow of tumor-bearing mice resulted in significantly prolonged survival and delayed tumor growth. Tumor progression was associated with change of the balance Th1/Th2 cells in favor of the Th2-like cytokine profile, while effective immunization was associated with a shift to the Th1 phenotype. Thus, frequent immunization of mice with mutant p53 peptide-pulsed DC generated from stem cells of tumor-bearing hosts can induce effective antitumor CTL responses associated with production of Th1 cells and lead to significant antitumor effects.

MeSH

[Amino Acid Sequence](#) ; [Animal](#) ; [Antigens, Neoplasm](#) ; [Bone Marrow](#) ; [Cell Differentiation](#) ; [Cytokines](#) ; [Dendritic Cells](#) ; [Female](#) ; [Hematopoietic Stem Cell Transplantation](#) ; [Immunotherapy, Adoptive](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Mice, Inbred C57BL](#) ; [Molecular Sequence Data](#) ; [Neoplasms, Experimental](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ;

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 [J Exp Med](#)

 [Volume 187](#)

[Issue 8](#)

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T helper 1 (Th1) and Th2 characteristics start to develop during T cell priming and are associated with an immediate ability to induce immunoglobulin class switching.

[Toellner KM](#), [Luther SA](#), [Sze DM](#), [Choy RK](#), [Taylor DR](#), [MacLennan ICM](#), [Acha-Orbea H](#)

J Exp Med 1998 Apr 20 **187**:8 1193-204

Abstract

The respective production of specific immunoglobulin (Ig)G2a or IgG1 within 5 d of primary immunization with Swiss type mouse mammary tumor virus [MMTV(SW)] or haptenated protein provides a model for the development of T helper 1 (Th1) and Th2 responses. The antibody-producing cells arise from cognate T cell B cell interaction, revealed by the respective induction of Cgamma2a and Cgamma1 switch transcript production, on the third day after immunization. T cell proliferation and upregulation of mRNA for interferon gamma in response to MMTV(SW) and interleukin 4 in response to haptenated protein also starts during this day. It follows that there is minimal delay in these responses between T cell priming and the onset of cognate interaction between T and B cells leading to class switching and exponential growth. The Th1 or Th2 profile is at least partially established at the time of the first cognate T cell interaction with B cells in the T zone. The addition of killed Bordetella pertussis to the hapten-protein induces nonhapten-specific IgG2a and IgG1 plasma cells, whereas the anti-hapten response continues to be IgG1 dominated. This indicates that a Th2 response to hapten-protein can proceed in a node where there is substantial Th1 activity.

MeSH

[Animal](#) ; [Bordetella pertussis](#) ; [Gamma-Globulins](#) ; [Germinal Center](#) ; [Haptens](#) ; [Immunoglobulin Class Switching](#) ; [Interferon Type II](#) ; [Interleukin-4](#) ; [Lymph Nodes](#) ; [Lymphocyte Transformation](#) ; [Mammary Tumor Viruses, Mouse](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Plasma Cells](#) ; [Spleen](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Vaccination](#) ;

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 [Nippon Rinsho](#)

 [Volume 55](#)

[Issue 6](#)

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[T cell vaccination--induction of anti-idiotypic immune response against TCR and shift of Th1/Th2 balance]

[Kakimoto K](#), [Hara H](#)

Nippon Rinsho 1997 Jun **55**:6 1512-8

Abstract

T cell vaccination, originally contrived and coined by I.R. Cohen is the injection of autoimmune pathogenic T cell line/clone or T cell receptor peptides in an attempt to induce anti-idiotypic regulation to treat autoimmune disease. Establishment of many T cell lines/clones from various autoimmune animal model and successful injection of these cells as T cell vaccine have been reported, although the exact mechanism for vaccination effect has not been elucidated. However, recent reports suggest that not the clonal deletion or anergy but the shift of Th1/Th2 balance of disease-related T lymphocytes may be involved in the effect of vaccination.

MeSH

[Animal](#) ; [Autoimmune Diseases](#) ; [English Abstract](#) ; [Human](#) ; [Immunotherapy, Active](#) ; [Receptors,](#)

[Antigen, T-Cell](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ;

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[Immunology](#)

[Volume 82](#)
[Issue 4](#)

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The role of TNF-alpha in T-cell-mediated inflammation depends on the Th1/Th2 cytokine balance.

[Hernandez-Pando R](#), [Rook GA](#)

Immunology 1994 Aug **82**:4 591-5

Abstract

The role of tumour necrosis factor-alpha (TNF-alpha) in tuberculosis is paradoxical because although there is much evidence for a protective role, there is also evidence that it plays a part in the tissue damage that characterizes human disease. We have shown previously that TNF-alpha frequently induces necrosis when injected into sites undergoing delayed-type hypersensitivity (DTH) responses to mycobacterial antigen. This is dependent on CD4+ T cells. However the presence of this sensitivity to TNF-alpha-induced necrosis depended on the immunization protocol. We have tested the hypothesis that sensitivity to TNF-alpha depends on the cytokine profile of the induced T-cell response. All subcutaneous doses of mycobacterial immunogen used (10(7) to 10(9) organisms) primed spleen cells so that they secreted interferon-gamma (IFN-gamma) and interleukin-2 (IL-2) when cultured in vitro with soluble antigen. However priming for production of IL-4 was dose dependent as in other systems, and was produced at all times from 7 to 30 days after immunization with 10(9) organisms. Time-course studies over 30 days showed that sensitivity to TNF-alpha was found in DTH sites of animals primed for IL-4 and IFN-gamma production, but not in animals primed only for the Th1 cytokines. We suggest therefore that the paradoxical role of TNF-alpha can be resolved. In 'pure' Th1 responses it may act as an additional macrophage-activating factor. In mixed Th1 + Th2 or Th0 responses it may cause tissue damage. This mixed pattern is characteristic of tuberculosis, and of the late stage of many chronic infections where elimination of the infecting organism is failing, and chronic tissue damage is seen.

MeSH

[Animal](#) ; [Antigens, Bacterial](#) ; [Cytokines](#) ; [Dose-Response Relationship, Immunologic](#) ; [Hypersensitivity, Delayed](#) ; [Immunization](#) ; [Interferon Type II](#) ; [Interleukin-4](#) ; [Kinetics](#) ; [Mice](#) ; [Mice, Inbred C57BL](#) ; [Mycobacterium](#) ; [Recombinant Proteins](#) ; [Support, Non-U.S. Gov't](#) ; [T-Lymphocytes, Helper-Inducer](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Tumor Necrosis Factor](#) ;

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[J Immunol](#)

[Volume 146](#)
[Issue 5](#)

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Comparison of Th1- and Th2-associated immune reactivities stimulated by single versus multiple vaccination of mice with irradiated *Schistosoma mansoni* cercariae.

[Caulada-Benedetti Z](#), [al-Zamel F](#), [Sher A](#), [James S](#)

J Immunol 1991 Mar 1 **146**:5 1655-60

Abstract

Mice immunized against *Schistosoma mansoni* by a single percutaneous exposure to radiation-attenuated parasite larvae demonstrate partial resistance to challenge infection that has been shown to correlate with development of cell-mediated immunity, whereas mice hyperimmunized by multiple exposure to attenuated larvae produce antibodies capable of

transferring partial protection to naive recipients. Measurement of Ag-specific lymphokine responses in these animals suggested that the difference in resistance mechanisms may be due to the differential induction of Th subset response by the two immunization protocols. Thus, upon Ag stimulation, singly immunized mice predominantly demonstrated responses associated with Th1 reactivity, including IL-2 and IFN-gamma production, whereas multiply immunized animals showed increased IL-5, IL-4, and IgG1 antibody production associated with enhanced Th2 response. These responses demonstrated some degree of organ compartmentalization, with splenocytes demonstrating higher Th1-related lymphokine production and cells from draining lymph nodes showing stronger proliferation and Th2 type reactivity. However, hyperimmunized mice also continued to demonstrate substantial Th1-associated immune reactivity. Moreover, in vivo Ag challenge elicited activated larvacidal macrophages in hyperimmunized animals. These observations indicate that protective cell-mediated mechanisms associated with induction of CD4+ Th1 cell reactivity predominate in singly vaccinated mice. Further vaccination stimulates Th2 responses, such as enhanced IgG1 production, that may also contribute to protective immunity.

MeSH

[Animal](#) ; [Antibodies, Helminth](#) ; [Antibody Specificity](#) ; [Comparative Study](#) ; [CD4-Positive T-Lymphocytes](#) ; [Female](#) ; [Immunoglobulin Isotypes](#) ; [Larva](#) ; [Lymphokines](#) ; [Macrophage Activation](#) ; [Mice](#) ; [Mice, Inbred C57BL](#) ; [Schistosoma mansoni](#) ; [Support, Non-U.S. Gov't](#) ; [T-Lymphocytes, Helper-Inducer](#) ; [Vaccination](#) ;

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Partial correction of the TH2/TH1 imbalance in neonatal murine responses to vaccine antigens through selective adjuvant effects.

[Barrios C](#), [Brandt C](#), [Berney M](#), [Lambert PH](#), [Siegrist CA](#)

Eur J Immunol 1996 Nov **26**:11 2666-70

Abstract

We have recently shown that neonatal responses to a pannel of vaccine antigens and presentation systems differed qualitatively from adult responses by a bias towards a TH2 pattern. Here we report that a selected adjuvant comprising block copolymers in a water-in-oil emulsion can induce balanced TH1/TH2 responses in BALB/c mice primed at 1 week of age with an immunodominant tetanus peptide vaccine. However, using this specific TH1-driving adjuvant only at time of boosting was not sufficient to fully circumvent the persisting influence of TH2-biased neonatal responses. Unexpectedly also, a significant local toxicity was observed in newborn and young mice, whereas only mild reactions occurred in adults. Thus, although the induction of strong TH1 responses in the neonatal period can be achieved using specific adjuvants, through modulation of the immunological environment present at time of priming, whether such immunization strategies would be safe in the neonatal period remains to be demonstrated. These observations should be taken into consideration in the development of novel vaccines that will have to be already effective early in life.

MeSH

[Adjuvants, Immunologic](#) ; [Alum Compounds](#) ; [Animal](#) ; [Animals, Newborn](#) ; [Bacterial Vaccines](#) ; [Cytokines](#) ; [Immunologic Memory](#) ; [Interferon Type II](#) ; [Interleukin-4](#) ; [Interleukin-5](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Poloxalene](#) ; [Support, Non-U.S. Gov't](#) ; [Tetanus Toxin](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ;

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Suppressive vaccination with DNA encoding a variable region gene of the T-cell receptor prevents autoimmune encephalomyelitis and activates Th2 immunity [see comments]

[Waisman A](#), [Ruiz PJ](#), [Hirschberg DL](#), [Gelman A](#), [Oksenberg JR](#), [Brocke S](#), [Mor F](#), [Cohen IR](#), [Steinman L](#)

Nat Med 1996 Aug 2:8 899-905

Abstract

A variable region gene of the T-cell receptor, V beta 8.2, is rearranged, and its product is expressed on pathogenic T cells that induce experimental autoimmune encephalomyelitis (EAE) in H-2u mice after immunization with myelin basic protein (MBP). Vaccination of these mice with naked DNA encoding V beta 8.2 protected mice from EAE. Analysis of T cells reacting to the pathogenic portion of the MBP molecule indicated that in the vaccinated mice there was a reduction in the Th1 cytokines interleukin-2 (IL-2) and interferon-gamma. In parallel, there was an elevation in the production of IL-4, a Th2 cytokine associated with suppression of disease. A novel feature of DNA immunization for autoimmune disease, reversal of the autoimmune response from Th1 to Th2, may make this approach attractive for treatment of Th1-mediated diseases like multiple sclerosis, juvenile diabetes and rheumatoid arthritis.

MeSH

[Amino Acid Sequence](#) ; [Animal](#) ; [Base Sequence](#) ; [Cytokines](#) ; [DNA](#) ; [DNA Primers](#) ; [Encephalomyelitis, Allergic](#) ; [Female](#) ; [Lymphocyte Transformation](#) ; [Mice](#) ; [Molecular Sequence Data](#) ; [Rats](#) ; [Receptors, Antigen, T-Cell, alpha-beta](#) ; [Support, Non-U.S. Gov't](#) ; [Support, U.S. Gov't, P.H.S.](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Vaccines](#) ;

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[J Infect Dis](#)

[Volume 177](#)

[Issue 1](#)

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Induction of Th2 cytokine expression for p27-specific IgA B cell responses after targeted lymph node immunization with simian immunodeficiency virus antigens in rhesus macaques.

[Kawabata S](#), [Miller CJ](#), [Lehner T](#), [Fujihashi K](#), [Kubota M](#), [McGhee JR](#), [Imaoka K](#), [Hiroi T](#), [Kiyono H](#)

J Infect Dis 1998 Jan 177:1 26-33

Abstract


To determine if there is an association between the isotype of simian immunodeficiency virus (SIV)-specific B cell responses and the profile of Th1 and Th2 cytokine expression, rhesus macaques were immunized with SIV antigens via the iliac lymph nodes, using a targeted lymph node (TLN) immunization procedure. When CD4+ T cells purified from antigen-stimulated peripheral blood mononuclear cells were analyzed, the levels of Th2 cytokine production were gradually increased after the second and third immunizations. However, interferon-gamma production did not change. Analysis of SIV-specific B cell responses revealed that the main isotype was IgG after the second and third immunizations. In addition, a peak of SIV-specific IgA B cell responses was noted following the third immunization. These findings suggest that the induction of Th2 type responses in TLN-immunized rhesus macaques reflects the sequence of initial induction of SIV-specific IgG-producing cells followed by IgA-secreting cells.

MeSH

[Animal](#) ; [Antibodies, Viral](#) ; [Antigens, CD4](#) ; [Antigens, Viral](#) ; [B-Lymphocytes](#) ; [Cells, Cultured](#) ; [Cytokines](#) ; [Female](#) ; [Flow Cytometry](#) ; [Gene Expression](#) ; [Gene Products, gag](#) ; [HIV Envelope Protein gp120](#) ; [IgA](#) ; [IgG](#) ; [Interferon Type II](#) ; [Interleukin-2](#) ; [Interleukin-4](#) ; [Interleukin-6](#) ; [Leukocytes, Mononuclear](#) ; [Lymph Nodes](#) ; [Macaca mulatta](#) ; [Polymerase Chain Reaction](#) ; [RNA, Messenger](#) ; [Support, Non-U.S. Gov't](#) ; [Support, U.S. Gov't, P.H.S.](#) ; [SIV](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Vaccination](#) ;

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 [Dev Biol Stand](#)

 [Volume 89](#)

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Bordetella pertussis-specific Th1/Th2 cells generated following respiratory infection or immunization with an acellular vaccine: comparison of the T cell cytokine profiles in infants and mice.

[Ryan M](#), [Gothefors L](#), [Storsaeter J](#), [Mills KH](#)

Dev Biol Stand 1997 **89**: 297-305

Abstract


In an investigation of cell-mediated immunity against *Bordetella pertussis*, we found that *B. pertussis* infection in infants and in mice was associated with the induction of antigen-specific T cells that secrete IFN-g and IL-2, but not IL-4 or IL-5. This cytokine profile is characteristic of Th1 cells that mediate cellular immune responses against a range of intracellular pathogens. An examination of cytokine production following immunization with a three-component acellular vaccine, comprising inactive PT, FHA and pertactin adsorbed to alum, demonstrated that spleen cells from vaccinated mice produced high levels of IL-5, but no detectable IFN-g and low levels of IL-2. In contrast, peripheral blood mononuclear cells from vaccinated infants produced IL-2, IL-5 and IFN-g. These findings highlight significant differences in the immune responses generated by vaccination and natural infection with *B. pertussis* and demonstrate that the T-cell response induced with an acellular vaccine, although dominated by type 2 cytokines in mice, is more heterogeneous in infants with a Th0 or mixed Th1/Th2 cytokine profile.

MeSH

[Adult](#) ; [Animal](#) ; [Antibodies, Bacterial](#) ; [Bordetella pertussis](#) ; [Comparative Study](#) ; [Cytokines](#) ; [Diphtheria-Tetanus-Pertussis Vaccine](#) ; [Human](#) ; [Immunity, Cellular](#) ; [Infant](#) ; [Mice](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Vaccination](#) ; [Whooping Cough](#) ;

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 [J Immunol](#)

 [Volume 156](#)

[Issue 12](#)

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Induction of Th1 cell-mediated protective immunity to *Schistosoma mansoni* by co-administration of larval antigens and IL-12 as an adjuvant.

[Mountford AP](#), [Anderson S](#), [Wilson RA](#)

J Immunol 1996 Jun 15 **156**:12 4739-45

Abstract

In this study, rIL-12, which is a powerful inducer of Th1 lymphocyte development, was administered to mice as an adjuvant in conjunction with a soluble lung-stage Ag preparation (SLAP) derived from lung-stage larvae of *Schistosoma mansoni* to potentiate Th1-mediated immune responses and induce resistance to reinfection. Immunization of mice with one or two doses of SLAP + IL-12 elicited a dominant population of Ag-specific Th1 lymphocytes in the draining lymph nodes, as judged by the secretion of abundant IFN-gamma but undetectable levels of IL-4, upon antigenic restimulation in vitro. In contrast, SLAP alone induced a mixed population of Th1 and Th2 cells with secretion of IFN-gamma, IL-4, and IL-10. The development of a biased Th1 cell population in mice immunized with SLAP + IL-12 was reflected in enhanced levels of Ag-specific IgG2a but decreased levels of IgG1 and total IgE serum Abs. Ablation of NK1.1+ cells before the administration of a single dose of SLAP + IL-12 reduced Th cell proliferation and almost completely inhibited secretion of IFN-gamma by in vitro-cultured lymph node cells. This indicates that NK cells stimulated by IL-12 shortly after vaccination are critical to the subsequent development of Ag-specific Th1 cells. Finally, it is demonstrated that the delivery of two doses of SLAP + IL-12 to mice is sufficient to elicit moderate but highly significant levels of protective immunity against challenge infection.


MeSH

[Adjuvants, Immunologic](#) ; [Animal](#) ; [Antibodies, Helminth](#) ; [Antigens, Helminth](#) ; [Cytokines](#) ; [Female](#) ; [Immunity, Cellular](#) ; [Immunoglobulin Isotypes](#) ; [Interleukin-12](#) ; [Killer Cells, Natural](#) ; [Lymphocyte Transformation](#) ; [Mice](#) ; [Mice, Inbred C57BL](#) ; [Schistosoma mansoni](#) ; [Schistosomiasis mansoni](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Vaccines](#) ;

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[Issue 8](#)

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Brucella abortus induces a novel cytokine gene expression pattern characterized by elevated IL-10 and IFN-gamma in CD4+ T cells.

[Svetic A](#), [Jian YC](#), [Lu P](#), [Finkelman FD](#), [Gause WC](#)

Int Immunol 1993 Aug **5**:8 877-83

Abstract

Immunization of BALB/c mice with killed *Brucella abortus* (BA) has previously been shown to increase serum IgG2a levels and long-term T cell clones from these mice secrete Th1-associated cytokines: IFN-gamma and IL-2 but not IL-4 or IL-5. We analyzed cytokine gene expression following primary immunization with BA to determine when CD4+ T cells first express cytokine genes and whether specific hypothesized cytokine patterns (e.g. Th precursor, Th0) could be identified prior to a Th1-like pattern. Our results demonstrated a highly consistent and novel pattern of Th1/Th2 cytokine gene expression characterized by elevated IL-10 and IFN-gamma in CD4+ T cells which rapidly manifests itself and is sustained for at least 10 days after immunization. No elevation in IL-2 cytokine gene expression was observed and treatment of BA-immunized mice with blocking anti-IL-2 antibodies had no effect on the cytokine gene expression pattern, although treatment with anti-IFN antibodies resulted in increased IL-4, IL-5, and IL-9 cytokine gene expression, in the absence of any change in IFN-gamma or IL-10 as early as 4 days after immunization. These results suggest that a whole pathogen may trigger sufficient costimulatory signals to rapidly induce effector T cells in the absence of elevated IL-2 and that IL-10 is specifically elevated in certain Th1-like responses.

MeSH

[Animal](#) ; [Brucella abortus](#) ; [CD4-Positive T-Lymphocytes](#) ; [Female](#) ; [Gene Expression Regulation](#) ; [Immunization](#) ; [Interferon Type II](#) ; [Interleukin-10](#) ; [Interleukin-2](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Support, U.S. Gov't, Non-P.H.S.](#) ; [Support, U.S. Gov't, P.H.S.](#) ; [T-Lymphocytes, Helper-Inducer](#) ;

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 [Immunol Cell Biol](#)

 [Volume 75](#)

[Issue 4](#)

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DNA vaccines for the treatment of autoimmune disease.

[Ramshaw IA](#), [Fordham SA](#), [Bernard CC](#), [Maguire D](#), [Cowden WB](#), [Willenborg DO](#)

Immunol Cell Biol 1997 Aug **75**:4 409-13

Abstract

DNA vaccines represent one of the most significant developments in vaccine technology in recent years. Although, in general, studies have primarily focused on the induction of protective immune responses against infectious pathogens, the technology may prove useful for other immune-related diseases, including autoimmunity. Autoimmune disease results from a breakdown in tolerance to self antigens; however, the same fundamental immunological reactions that

control immune responses to foreign antigens are also likely to operate during the course of autoimmune disease. These include the reciprocal regulation of Th cell subsets. Th1 cells appear to be involved in many organ-specific autoimmune diseases while suppression of disease is associated with cells of the Th2 phenotype. It has been possible, therefore, to suppress many of the pathological consequences of autoimmunity by manipulating the Th1/Th2 cell balance. The induction of Th2 responses by DNA immunization might therefore be expected to have a profound effect on the course of autoimmune disease. Indeed, we have demonstrated that DNA immunization can protect animals against the autoimmune central nervous system inflammatory disease, experimental autoimmune encephalomyelitis (EAE). As many other autoantigens have now been identified, the application of this technology to other autoimmune diseases warrants investigation.

MeSH

[Animal](#) ; [Encephalomyelitis, Allergic](#) ; [Rats](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Vaccines, DNA](#) ;

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 [Volume 19](#)

[Issue 1](#)

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IL-12 eliminates the Th-2 dependent protective immune response of mice to larval *Strongyloides stercoralis*.

[Rotman HL](#), [Schnyder-Candrian S](#), [Scott P](#), [Nolan TJ](#), [Schad GA](#), [Abraham D](#)

Parasite Immunol 1997 Jan **19**:1 29-39

Abstract

The goal of the present study was to determine if immune-mediated killing of *S. stercoralis* L3 in mice could be modulated by shifting from a Th-2 to a Th-1 type immune response. L3 killing in immunized mice was ablated in CD4+ T cell-depleted animals, but not in CD8+ T cell-depleted or beta 2-microglobulin-deficient mice. Treatment of immunized mice with IL-4 or IL-5 neutralizing MoAb significantly reduced the protective effects of vaccination against *S. stercoralis*, while protective immunity was unimpaired in IFN-gamma knockout mice. Recombinant IL-12 was administered to infected mice to switch the immune response from a Th-2 to a Th-1 type response. Protective immunity was ablated in immunized mice that received IL-12 therapy. Eosinophil numbers, eosinophil peroxidase levels, and parasite-specific IgG1 levels were lowered in IL-12 treated immunized animals, and parasite-specific IgG2a levels were increased in these animals. The data indicate that eosinophils are important as mediators of larval killing, and that the establishment of Th-2 type immunity results in killing of infective *S. stercoralis* L3, while a shift to Th-1 type immunity abrogates protective responses.

MeSH

[Animal](#) ; [CD8-Positive T-Lymphocytes](#) ; [Dogs](#) ; [Enzyme-Linked Immunosorbent Assay](#) ; [Immunity](#) ; [Immunization](#) ; [Interleukin-12](#) ; [Interleukin-4](#) ; [Interleukin-5](#) ; [Larva](#) ; [Lymphocyte Depletion](#) ; [Male](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Mice, Inbred C57BL](#) ; [Peroxidases](#) ; [Strongyloides stercoralis](#) ; [Strongyloidiasis](#) ; [Support, Non-U.S. Gov't](#) ; [Support, U.S. Gov't, P.H.S.](#) ; [T-Lymphocytes, Helper-Inducer](#) ; [Th2 Cells](#) ;

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Th1 and Th2 subsets: paradigms lost?

[Kelso A](#)

Immunol Today 1995 Aug **16:8** 374-9

Abstract


The T helper 1 (Th1)/Th2 model has provided a valuable framework to investigate and explain many immune reactions and now pervades current thinking on the regulatory role of T cells. However, individual T cells and clones display remarkable diversity in their cytokine profiles, collectively forming a continuous spectrum in which Th1 and Th2 cells may be only two of the possible extreme phenotypes. For these reasons, Anne Kelso argues that cytokine-producing T cells cannot be classified into discrete subsets.

MeSH

[Animal](#) ; [Clone Cells](#) ; [Cytokines](#) ; [Gene Expression Regulation](#) ; [Immunization](#) ; [Immunophenotyping](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Mice, Inbred C57BL](#) ; [Mice, Inbred DBA](#) ; [Models, Immunological](#) ; [Support, Non-U.S. Gov't](#) ; [T-Lymphocyte Subsets](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ;

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Vaccination of the Leishmania major susceptible BALB/c mouse. I. The precise selection of peptide determinant influences CD4+ T cell subset expression.

[Soares LR](#), [Sercarz EE](#), [Miller A](#)

Int Immunol 1994 May **6:5** 785-94

Abstract

BALB/c mice are susceptible to cutaneous leishmaniasis upon infection with *Leishmania major* while C57BL/6 are not. There is a major promastigote surface protease (PSP or gp63) which is available in both native and recombinant forms, and for which the primary amino acid sequence is known. Immunization with PSP has been shown to offer some protection against challenge with the live organism. Therefore, we attempted to develop a peptide vaccine with PSP peptides. In the first experiments, recall proliferative responses to PSP were measured using a set of 15mer peptides spanning the entire PSP molecule which allowed designation of major determinant regions in BALB/c, C57BL/6, and CBA mice. Several of these determinants were promiscuous and shared almost the identical core amino acid residues in the different strains. Immunization with major determinant peptides was recalled vigorously with *L. major* soluble antigen as well as with PSP. The response to peptide was almost entirely Th1 as measured by a localized ELISA assay for single-cell production of IFN-gamma. A similar assay for IL-5, which overcomes problems of sensitivity and inhibition by lymphokines produced by Th1 cells, indicates very little production of Th2 cells even by BALB/c. It was found that if a major responsive peak was examined by recall with overlapping peptides, the highest, central peptide gave a mainly Th1 response while the boundary, less efficient peptides gave more of a Th2 response. Possible reasons for this were discussed. These results point to the importance of selecting the exactly appropriate peptide in considering a vaccino-gen that might protect susceptible individuals. Even the choice of a somewhat immunogenic peptide within the determinant envelope might actually exacerbate infection by steering the response in a Th2 direction.

MeSH

[Amino Acid Sequence](#) ; [Animal](#) ; [CD4-Positive T-Lymphocytes](#) ; [Epitopes](#) ; [Female](#) ; [Leishmania major](#) ; [Leishmaniasis, Cutaneous](#) ; [Lymphocyte Transformation](#) ; [Metalloproteinases](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Mice, Inbred CBA](#) ; [Mice, Inbred C57BL](#) ; [Molecular Sequence Data](#) ; [Peptides](#) ; [Protozoan Proteins](#) ; [Protozoan Vaccines](#) ; [Support, Non-U.S. Gov't](#) ; [Support, U.S. Gov't, P.H.S.](#) ; [T-Lymphocyte Subsets](#) ; [Vaccination](#) ;

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 [Volume 14](#)

A TH1-->TH2 switch is a critical step in the etiology of HIV infection [see comments]

[Clerici M](#), [Shearer GM](#)

Immunol Today 1993 Mar 14:3 107-11

Abstract


This viewpoint proposes that an imbalance in the TH1-type and TH2-type responses contributes to the immune dysregulation associated with HIV infection, and that resistance to HIV infection and/or progression to AIDS is dependent on a TH1-->TH2 dominance. This hypothesis is based on the authors' findings that: (1) progression to AIDS is characterized by loss of IL-2- and IFN-gamma production concomitant with increases in IL-4 and IL-10; and (2) many seronegative, HIV-exposed individuals generate strong TH1-type responses to HIV antigens.

MeSH

[Acquired Immunodeficiency Syndrome](#) ; [Animal](#) ; [AIDS Vaccines](#) ; [CD4-Positive T-Lymphocytes](#) ; [Haplorhini](#) ; [Human](#) ; [HIV Infections](#) ; [Immunization](#) ; [Interferon Type II](#) ; [Interleukins](#) ; [Male](#) ; [Mice](#) ; [Models, Biological](#) ; [SIV](#) ; [T-Lymphocytes, Helper-Inducer](#) ;

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Cyclophosphamide given after active specific immunization augments antitumor immunity by modulation of Th1 commitment of CD4+ T cells.

[Li L](#), [Okino T](#), [Sugie T](#), [Yamasaki S](#), [Ichinose Y](#), [Kanaoka S](#), [Kan N](#), [Imamura M](#)

J Surg Oncol 1998 Apr 67:4 221-7

Abstract

BACKGROUND AND OBJECTIVES: In order to evaluate the regulatory effect of cyclophosphamide (CPA) on active specific immunization (ASI)-induced antitumor immunity, we examined the timing of CPA (100 mg/kg) with ASI, and focused on whether CPA given after ASI augments antitumor immunity by modulation of Th1 commitment of CD4+ T cells. **METHODS:** We examined the effect of CPA combined with ASI using sonicated tumor supernatant (SS) and recombinant interleukin-1 beta (rIL-1 beta). **RESULTS:** Survival of i.p. tumor inoculated mice after ASI (days -12, -9, and -6) followed by 100 mg/kg CPA (day -3) (ASI-CPA) was significantly prolonged compared with that of mice treated with ASI alone, whereas CPA (day -15) treatment before ASI (CPA-ASI) completely abrogated the survival prolongation by ASI alone. In early stage (day 0) after ASI-CPA treatment, the CD4+ T cells were determined to play an important role in the protective immunity for the following reasons: 1) the CD4+/CD8+ ratio of spleen cells from immunized mice was higher than that of the control or CPA alone treated group; and 2) the tumor neutralizing activity of fresh spleen cells was abrogated by CD4+ T-cell depletion in vitro. CD4+ T cells of mice treated with ASI-CPA produced more interferon (IFN)-gamma and IL-2 and less IL-4 than those of the ASI alone group. **CONCLUSIONS:** These results suggest that the protective immunity induced by ASI was augmented through the modification of the Th1 and Th2 balance by CPA injection after ASI.


MeSH

[Animal](#) ; [Cyclophosphamide](#) ; [CD4-CD8 Ratio](#) ; [CD4-Positive T-Lymphocytes](#) ; [Flow Cytometry](#) ; [Immunity, Cellular](#) ; [Interferon Type II](#) ; [Interleukin-2](#) ; [Male](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Plasmacytoma](#) ; [Spleen](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Vaccination](#) ;

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 [Volume 154](#)

Vaccination routes that fail to elicit protective immunity against *Schistosoma mansoni* induce the production of TGF-beta, which down-regulates macrophage antiparasitic activity.

[Williams ME](#), [Caspar P](#), [Oswald I](#), [Sharma HK](#), [Pankewycz O](#), [Sher A](#), [James SL](#)

J Immunol 1995 May 1 **154**:9 4693-700

Abstract

C57BL/6 mice immunized intradermally (i.d.) with bacillus Calmette Guerin (BCG) plus killed skin-stage schistosomula are protected against subsequent infection with *Schistosoma mansoni*, whereas immunization by i.v. or i.m. routes is not protective. Moreover, previous immunization via the nonprotective i.v. route interfered with the ability to subsequently induce protection by i.d. vaccination, suggesting that inhibitory responses are invoked. Given the evidence that activated macrophages (M phi) play a role as effector cells in protection against schistosomiasis, we investigated the ability of spleen cells from protected and nonprotected immunized mice to produce M phi activating and deactivating cytokines. Exposure to supernatant fluids (SNs) from Ag stimulated spleen cells of i.d., but not i.v. or i.m., immunized mice activated inflammatory M phi for in vitro killing of schistosome larvae, through a mechanism dependent on both IFN gamma and TNF-alpha. No evidence was observed for the preferential induction of the M phi activating Th1 cytokines IFN-gamma and IL-2 in i.d. immunized mice, nor did spleen cells from nonprotected animals produce higher levels of the Th2 associated cytokines IL-4 and IL-10, which are known to prevent M phi activation. TGF-beta was, however, detected in SNs from unprotected mice. Moreover, the M phi inhibitory activity detected in these SNs was heat stable and neutralized by anti-TGF-beta Abs, suggesting that production of TGF-beta is at least partially responsible for the failure of i.m. and i.v. immunized mice to develop immunity to *S. mansoni*. Thus, the induction of down-regulatory cytokines may be an important factor limiting the efficacy of certain vaccination protocols.

MeSH

[Animal](#) ; [BCG Vaccine](#) ; [Cells, Cultured](#) ; [Culture Media, Conditioned](#) ; [Cytokines](#) ; [Down-Regulation \(Physiology\)](#) ; [Female](#) ; [Injections, Intradermal](#) ; [Injections, Intramuscular](#) ; [Injections, Intravenous](#) ; [Macrophages](#) ; [Mice](#) ; [Mice, Inbred C57BL](#) ; [Schistosomiasis mansoni](#) ; [Spleen](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Transforming Growth Factor beta](#) ; [Vaccination](#) ;

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Immunization of non-obese diabetic (NOD) mice with glutamic acid decarboxylase-derived peptide 524-543 reduces cyclophosphamide-accelerated diabetes.

[Sai P](#), [Rivereau AS](#), [Granier C](#), [Haertlé T](#), [Martignat L](#)

Clin Exp Immunol 1996 Aug **105**:2 330-7

Abstract

NOD mice constitute a model for studying the prevention of human autoimmune type 1 diabetes. Glutamic acid decarboxylase (GAD) could be a key antigen involved in this disease, and GAD65 peptide 524-543 has been implicated in early T cell response in young NOD mice. We performed two i.p. injections of GAD peptide 524-543 (100 micrograms at each injection), together with Freund's incomplete adjuvant (FIA), into female NOD mice at 30 and 45 days old. Diabetes was accelerated 2 weeks later by a single injection of cyclophosphamide (CY), which acts against suppressive mechanisms. Treatment with GAD 524-543 peptide delayed the onset of diabetes and reduced its incidence (28% versus 60%; $P < 0.001$) compared with control mice injected with FIA alone, or GAD peptide 534-553, or an irrelevant peptide. In the same group, the severity of lymphocytic inflammation of pancreatic islets was reduced ($P < 0.03$). Up to 3 months after peptide injections, a strong splenocytic proliferative response occurred in immunized NOD mice against the immunizing peptide alone (but not against a panel of seven other GAD65-derived peptides). After peptide challenge of splenocytes in vitro, protection against CY-accelerated diabetes was associated with higher peptide-specific production of T helper type 2 (Th2)-associated interleukins 4 and 10, whereas

Th1-associated interferon-gamma and IL-2 were proportionally less represented. During contransfer, T splenocytes from GAD 524-543-immunized mice were able to reduce the capacity of T cells from diabetic donors to transfer the disease adoptively ($P < 0.01$), demonstrating the generation of cellular mechanisms that actively suppress the disease. It is concluded that immunization of NOD mice with GAD65 peptide 524-543 can counteract CY-accelerated diabetes, possibly through active cellular suppression linked to a shift of Th1/Th2 balance toward the production of Th2 cytokines such as IL-4 and IL-10. This study provides additional support for the notion that GAD, and more precisely its epitope 524-543, could be one of the key targets for the pathogenesis of type 1 diabetes in NOD mice, as well as for the efficacy of disease-specific peptide therapy in type 1 diabetes.


MeSH

[Amino Acid Sequence](#) ; [Animal](#) ; [Cyclophosphamide](#) ; [Diabetes Mellitus, Insulin-Dependent](#) ; [Female](#) ; [Glutamate Decarboxylase](#) ; [Immunization](#) ; [Immunotherapy, Adoptive](#) ; [Interferon Type II](#) ; [Islets of Langerhans](#) ; [Lymphocytes](#) ; [Mice](#) ; [Mice, Inbred NOD](#) ; [Molecular Sequence Data](#) ; [Peptide Fragments](#) ; [Support, Non-U.S. Gov't](#) ;

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IL-12 enhances vaccine-induced immunity to *Schistosoma mansoni* in mice and decreases T helper 2 cytokine expression, IgE production, and tissue eosinophilia.

[Wynn TA](#), [Jankovic D](#), [Hieny S](#), [Cheever AW](#), [Sher A](#)

J Immunol 1995 May 1 **154**:9 4701-9

Abstract

Vaccination of mice with radiation-attenuated cercariae of *Schistosoma mansoni* results in a highly significant but partial protection against challenge infection. This immunity is dependent on CD4+ T cells, and because of its suppression by anti-IFN-gamma, appears to be caused by a Th1 response. Nevertheless, both Th1 and Th2 lymphokines are expressed in vaccinated and challenged mice, and we hypothesized that the expression of the latter group of down-regulatory cytokines may be responsible for the failure to obtain complete protection. Because IL-12 is a key cytokine that suppresses Th2-like responses, we asked whether IL-12 could increase vaccine-induced immunity to *S. mansoni*. Indeed, administration of IL-12 significantly reduced worm burdens following a challenge infection. IL-12-treated animals displayed a marked increase in pulmonary IFN-gamma and IL-12 p40 mRNA expression, while levels of IL-4, IL-5, and IL-13 were suppressed significantly during the period of vaccination. A marked decrease in serum IgE and tissue eosinophilia, two responses regulated by Th2 cytokines, was also observed. Surprisingly, IL-12-treated/vaccinated mice failed to demonstrate a significant increase in IFN-gamma, TNF-alpha, or nitric oxide synthase mRNA at the time of challenge infection when compared with vaccinated controls, but did, however, display significantly suppressed Th2 cytokine mRNA production. Together, these data demonstrate that exogenous IL-12 regulates Th1/Th2 responses during immunization with irradiated cercariae, and suggest that this cytokine may be used to increase vaccine-induced immunity to *S. mansoni*.

MeSH

[Animal](#) ; [Cytokines](#) ; [Eosinophils](#) ; [Female](#) ; [IgE](#) ; [Interleukin-12](#) ; [Lung](#) ; [Mice](#) ; [Mice, Inbred C57BL](#) ; [Polymerase Chain Reaction](#) ; [RNA, Messenger](#) ; [Schistosomiasis mansoni](#) ; [Th2 Cells](#) ; [Vaccines, Attenuated](#) ;

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Altered Th1/Th2 balance associated with the immunosuppressive/protective effect of the H-2Ab allele on the response to allo-4-hydroxyphenylpyruvate dioxygenase.

[Brunner M](#), [Larsen S](#), [Sette A](#), [Mitchison A](#)

Eur J Immunol 1995 Dec **25:12** 3285-9

Abstract

The H-2Ab allele exerts a dominant down-regulatory effect on the anti-allo-HPPD (4-hydroxyphenylpyruvate dioxygenase) antibody response, through a hitherto unknown mechanism. In the present study, the allo-variable peptide bound to responder H-2Ak molecules with higher affinity than to H-2Ab ones, arguing against the operation of an affinity hierarchy. Quantitative polymerase chain reaction revealed differences in cytokine mRNA expression between suppressed and high-responder mice. Lymph node cells of responder but not suppressed mice contained high levels of interleukin (IL)-4 mRNA as early as 11 h post-immunization and continued to do so for at least 8 days; this early burst was paralleled by a small burst in transforming growth factor (TGF)-beta mRNA level. Differences in IL-12 mRNA were not detected, although an early IL-12 effect could not be excluded. Interferon (IFN)-gamma appeared to contribute to the suppression at later time points. Early treatment of responder mice with anti-IL-4 monoclonal antibody (11B11) down-regulated the antibody response. The proliferative T cell response from hyperimmunized mice was reduced but still detectable in the presence of an H-2Ab allele. Thus, in the presence of this allele, the Th1 response is enhanced and that of Th2 cells suppressed, apparently as a result of the bias of H-2Ab-restricted T cells in favor of the Th1 subset.


MeSH

[Alleles](#) ; [Animal](#) ; [Antibody Formation](#) ; [Base Sequence](#) ; [Cytokines](#) ; [Female](#) ; [H-2 Antigens](#) ; [Immunophenotyping](#) ; [Immunosuppression](#) ; [Interleukin-4](#) ; [Mice](#) ; [Mice, Inbred CBA](#) ; [Molecular Sequence Data](#) ; [Protein Binding](#) ; [RNA, Messenger](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [4-Hydroxyphenylpyruvate Dioxygenase](#) ;

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An immunosuppressive murine leukaemia virus induces a Th1-->Th2 switch and abrogates the IgM antibody response to sheep erythrocytes by suppressing the production of IL-2.

[Faxvaag A](#), [Espevik T](#), [Dalen A](#)

Clin Exp Immunol 1995 Dec **102:3** 487-95

Abstract

Many retroviruses have tropism for cells in the immune system and have a propensity to induce immunosuppression in the host. Some of the effects of retroviruses on immune cell function are thought to be mediated through cytokines. Friend Immunosuppressive virus-2 (FIS-2) is a low oncogenic murine leukaemia virus (MuLV) that induces lymphadenopathy and immunosuppression in NMRI mice. The role of T cell cytokines during the generation of a primary antibody response in healthy and FIS-2-infected mice was studied following the antibody response to sheep erythrocytes by an in vitro immunization (IVI) technique. In cultures from FIS-2-infected mice, the antibody response was reduced compared with cultures from uninfected mice and the production of the Th2 cytokines IL-4 and IL-6 was elevated, whereas the Th1 cytokines IL-2, interferon-gamma (IFN-gamma) and tumour necrosis factor-alpha (TNF-alpha) were reduced. The suppressed anti-sheep erythrocyte antibody response in cultures from mice infected with FIS-2 seemed to be caused by an insufficient production of IL-2, since addition of recombinant IL-2 stimulated the antibody response. This effect was also observed in cultures depleted of T cells, indicating a direct effect of IL-2 on B cells. A switch to a Th2 cell response and suppression of IL-2 production might play a central role in the immune cell dysfunction induced by FIS-2.

MeSH

[Animal](#) ; [Antibody Formation](#) ; [Erythrocytes](#) ; [Female](#) ; [IgM](#) ; [Immune Tolerance](#) ; [Interleukin-2](#) ; [Leukemia Viruses, Murine](#) ; [Mice](#) ; [Sheep](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Transforming Growth](#)

[Factor beta](#) ; [Tumor Necrosis Factor](#) ;

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Idiotype-specific, major histocompatibility complex restricted T cells are of both Th1 and Th2 type.

[Lauritzsen GF](#), [Bogen B](#)

Scand J Immunol 1991 Jun **33:6** 647-56

Abstract

The lymphokine secretion patterns of seven independent 91-101.lambda 2(315)/I-Ed specific, CD4+ T-cell clones have been investigated. Six of the clones are of the Th1 type as they secrete IL2 and IFN gamma, but not IL4. Some of these six Th1 clones produce TNF alpha/beta, and some produce minor amounts of IL5 and IL6. One clone is of the Th2 type as it produces IL4, IL5, and large amounts of IL6, but not IL2, IFN gamma or TNF. The Th1/Th2 classification does not have any stringent relationship to immunization protocol, fine specificity and V alpha/V beta gene segment utilization. The immunoregulatory significance of our findings for Id/MHC-dependent T-B cell interaction is discussed.

MeSH

[Animal](#) ; [Antigens, Differentiation, T-Lymphocyte](#) ; [Clone Cells](#) ; [CD4-Positive T-Lymphocytes](#) ; [Enzyme-Linked Immunosorbent Assay](#) ; [Flow Cytometry](#) ; [Human](#) ; [Immunoglobulin Idiotypes](#) ; [Lymphocyte Transformation](#) ; [Lymphokines](#) ; [Major Histocompatibility Complex](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Receptors, Antigen, T-Cell](#) ; [Support, Non-U.S. Gov't](#) ; [T-Lymphocytes, Cytotoxic](#) ; [T-Lymphocytes, Helper-Inducer](#) ;

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[Volume 53](#)

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Prevalence of allergy in children in relation to prior BCG vaccination and infection with atypical mycobacteria.

[Strannegard IL](#), [Larsson LO](#), [Wennergren G](#), [Strannegard O](#)

Allergy 1998 Mar **53:3** 249-54

Abstract

By influence on the Th1/Th2 cell balance, infectious agents may affect the development of atopic allergy. In this study, we investigated whether previous BCG vaccination or infection with atypical mycobacteria might be related to the development of atopic disease. The study, which involved skin testing with mycobacteria and answers to a questionnaire for more than 6000 children in Sweden, revealed a low prevalence of allergy among BCG-vaccinated children who were immigrants or adopted from other countries. Vaccinated children born in Sweden, however, did not have significantly lower allergy prevalence than age-matched, unvaccinated children. Furthermore, the overall frequencies of skin-test reactivity to the atypical mycobacteria *M. avium* and *M. scrofulaceum* were higher rather than lower in allergic than in nonallergic children. By contrast, there was a tendency toward a lower frequency of more strongly positive skin reactions (> or = 10 mm) to mycobacteria in allergic than in nonallergic children. These findings do not support the hypothesis that early mycobacterial infections have a suppressive effect on the development of

atopic disease. Earlier findings of an apparent association between atopy and lack of previous mycobacterial infection may possibly be explained by a relatively decreased ability of atopic patients to mount strong Th1 cell-mediated immune responses.

MeSH

[BCG Vaccine](#) ; [Child](#) ; [Child, Preschool](#) ; [Human](#) ; [Hypersensitivity, Immediate](#) ; [Mycobacterium avium](#) ; [Mycobacterium scrofulaceum](#) ; [Mycobacterium Infections, Atypical](#) ; [Questionnaires](#) ; [Skin Tests](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Vaccination](#) ;

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Nucleic acid vaccine-induced immune responses require CD28 costimulation and are regulated by CTLA4.

[Horspool JH](#), [Perrin PJ](#), [Woodcock JB](#), [Cox JH](#), [King CL](#), [June CH](#), [Harlan DM](#), [St. Louis DC](#), [Lee KP](#)

J Immunol 1998 Mar 15 **160**:6 2706-14

Abstract

Immunization with plasmids expressing specific genes (DNA or nucleic acid vaccination (NAV)) elicits robust humoral and cell-mediated immune responses. The mechanisms involved in T cell activation by NAV are incompletely characterized. We have examined the costimulatory requirements of NAV. CD28-deficient mice did not mount Ab or CTL responses following i.m. immunization with eukaryotic expression plasmids encoding the bacterial gene beta-galactosidase (beta gal). Because these mice retained their ability to up-regulate the CTLA4 receptor (a negative regulator of T cell activation), we examined CTLA4's role in the response of wild-type BALB/c mice to NAV. Intact anti-CTLA4 mAb but not Fab fragments suppressed the primary humoral response to pCIA/beta gal without affecting recall responses, indicating CTLA4 activation inhibited Ab production but not T cell priming. Blockade of the ligands for CD28 and CTLA4, CD80 (B7-1) and CD86 (B7-2), revealed distinct and nonoverlapping function. Blockade of CD80 at initial immunization completely abrogated primary and secondary Ab responses, whereas blockade of CD86 suppressed primary but not secondary responses. Simultaneous blockade of CD80 + CD86 was less effective at suppressing Ab responses than either alone. Enhancement of costimulation via coinjection of B7-expressing plasmids augmented CTL responses but not Ab responses, and without evidence of Th1 to Th2 skewing. These findings suggest complex and distinct roles for CD28, CTLA4, CD80, and CD86 in T cell costimulation following nucleic acid vaccination.

MeSH

[Animal](#) ; [Antibody Formation](#) ; [Antigens, CD](#) ; [Antigens, CD28](#) ; [Antigens, CD80](#) ; [Antigens, Differentiation](#) ; [DNA, Complementary](#) ; [Immunization](#) ; [Lymphocyte Transformation](#) ; [Membrane Glycoproteins](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Support, Non-U.S. Gov't](#) ; [T-Lymphocytes](#) ; [T-Lymphocytes, Cytotoxic](#) ; [Vaccines, DNA](#) ;

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Pathogenesis of tuberculosis in mice exposed to low and high doses of an environmental mycobacterial saprophyte before infection.

Abstract

Mycobacteria are ubiquitous in the environment, but they are not part of the normal human microbial flora. It has been suggested that variable contact with mycobacteria can influence susceptibility to mycobacterial pathogens and the efficacy of subsequent Mycobacterium bovis BCG vaccination. To test this, mice were immunized with high or low doses of an environmental saprophyte, *M. vaccae*, that is intensely immunogenic as an autoclaved preparation. Two months later, they received an intratracheal challenge with *M. tuberculosis* H37Rv. Recipients of a low Th1-inducing dose (10(7) organisms) were partially protected and maintained a high ratio of interleukin 2 (IL-2)-positive to IL-4-positive cells in the perivascular, peribronchial, and granulomatous areas of the lung, whereas in unimmunized controls the IL-4-positive cells increased markedly between days 21 and 28. In contrast, recipients of the high dose (10(9) organisms), which primes Th2 as well as Th1 cytokine production, died more rapidly than unimmunized controls and showed massive pneumonia from day 7. The ratio of IL-2-positive to IL-4-positive cells in all compartments of the lung rapidly fell to 1 by day 14 for these animals. These events correlated with cytokine mRNA profiles and with increases in the local toxicity of tumor necrosis factor alpha (TNF-alpha), demonstrable only when a major Th2 component was present. These data indicate that cross-reactive epitopes present in an environmental saprophyte can evoke either protective responses or responses that increase susceptibility to *M. tuberculosis*. The latter are associated with the presence of a Th2 component and increased sensitivity to TNF-alpha.

MeSH

Animal ; Environmental Microbiology ; Hypersensitivity, Delayed ; Immunization ; Immunohistochemistry ; Interleukin-2 ; Interleukin-4 ; Male ; Mice ; Mice, Inbred BALB C ; Mycobacterium ; Support, Non-U.S. Gov't ; Th2 Cells ; Tuberculosis ; Tumor Necrosis Factor ;

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Thalidomide therapy of established collagen-induced arthritis (CIA) not accompanied by an evident Th2 shift.

Hauschild A, Kroeger H, Mitchison NA, Ugrinovic S, Zwingenberger K

Clin Exp Immunol 1997 Jun **108**:3 428-31

Abstract

Thalidomide, a drug likely to affect the cytokine pattern, was administered orally to mice at various stages of CIA. Treatment (150 mg/kg per day by gavage, 5 days/week), started 6 weeks post-immunization, i.e. at the height of the disease, significantly reduced arthritis, and appeared also to reduce the level of inflammation as judged by neutrophil chemiluminescence. With treatment started 9 weeks post-immunization the effect on arthritis was no longer statistically significant, and when started at 14 weeks was lost. Over a dose range of up to 150 mg/kg per day the treatment had no effect on either interferon-gamma (IFN-gamma) or IL-4 mRNA levels. The treatment is therefore not likely to have operated via a shift in the Th1/Th2 balance.

MeSH

Animal ; Arthritis ; Collagen ; Mice ; Mice, Inbred DBA ; Thalidomide ; Th1 Cells ; Th2 Cells ; Tumor Necrosis Factor ;

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 [Volume 90](#)

Vaccination with a multi-epitopic recombinant allergen induces specific immune deviation via T-cell anergy.

[Cao Y](#), [Yang M](#), [Luo Z](#), [Mohapatra SS](#)

Immunology 1997 Jan **90**:1 46-51

Abstract

Prophylactic vaccination has recently emerged as a major paradigm toward the prevention and therapy of allergies and asthma; however, the immunological basis of this approach remains to be elucidated. We examined the potential and mechanism of prophylaxis of allergic response in B6D2F1 mice with a multi-epitopic recombinant allergen, rKBG8.3 (MERA-8.3), which represents a major group of allergens of grass pollens, used herein as a model of MERA vaccine. Vaccination (subcutaneous) with soluble MERA-8.3, prior to immunization with the MERA-8.3 in alum, led to suppression of the IgE antibody response and a concomitant increase in IgG2a antibody response specific to the MERA-8.3 in a dose-dependent manner. Analysis of cytokine patterns in spleen and lymph node cells revealed a marked decrease of interleukin-2 (IL-2) and IL-4 production and to a lesser extent a decrease of interferon-gamma (IFN-gamma) synthesis, resulting in an increased ratio of IFN-gamma: IL-4 in vaccinated-immunized mice compared with untreated-immunized control mice. Furthermore, splenocytes of mice treated with the MERA-8.3 alone proliferated to MERA-8.3 in vitro with reduced capacity compared with the splenocytes of MERA-8.3-alum immunized mice, owing to a markedly reduced level of IL-2 production in the former. Collectively, these results suggest that vaccination with the MERA-8.3 induces T-cell anergy, which is pivotal to deviation of specific immunity from Th2- to Th1-like, and may serve as an important approach to prevention and therapy of allergic disorders.

MeSH

[Allergens](#) ; [Animal](#) ; [Clonal Anergy](#) ; [Cytokines](#) ; [Female](#) ; [IgE](#) ; [IgG](#) ; [Immune Tolerance](#) ; [Interleukin-2](#) ; [Mice](#) ; [Mice, Inbred C57BL](#) ; [Mice, Inbred DBA](#) ; [Polymerase Chain Reaction](#) ; [Recombinant Proteins](#) ; [RNA, Messenger](#) ; [Support, Non-U.S. Gov't](#) ; [T-Lymphocytes](#) ; [Vaccination](#) ; [Vaccines, Synthetic](#) ;

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Induction of T-cell immunity against Ras oncoproteins by soluble protein or Ras-expressing Escherichia coli [see comments]

[Fenton RG](#), [Keller CJ](#), [Hanna N](#), [Taub DD](#)

J Natl Cancer Inst 1995 Dec 20 **87**:24 1853-61

Abstract

BACKGROUND: Point mutations in the ras proto-oncogene that activate its oncogenic potential occur in approximately 30% of human cancers. Previous studies have demonstrated that T-cell immunity against some forms of mutant Ras proteins could be elicited, and some effectiveness against tumors expressing activated Ras has been reported. **PURPOSE:** The goal of this study was to determine if immunization of mice with two forms of mutant Ras protein can induce high levels of Ras mutation-specific T-cell immunity in vitro and tumor regression in vivo. **METHODS:** Mice (BALB/c or C3H/HeJ) were immunized subcutaneously at 2-week intervals with purified Ras oncoproteins mixed with the immunologic adjuvants Antigen Formulation or QS-21, both of which have been shown to enhance the induction of T-cell-mediated immunity when included as components of soluble protein vaccines. In some experiments, mice were immunized directly with heat-killed Escherichia coli that had been induced to express one of the mutant Ras proteins. Spleen cells plus lymph node cells from Ras-immunized mice were tested in vitro for lysis of syngeneic Ras-expressing tumor cells and proliferation in response to mutant Ras peptides. For some of the cytolytic activity experiments, the spleen cells were grown under TH1 conditions (growth in presence of interleukin 2, interferon gamma, and an antibody directed against interleukin 4 to stimulate a cell-mediated immune response) or TH2 conditions (growth in presence of interleukins 2 and 4 to stimulate a humoral immune response). The specificity of immunity was examined in vivo by challenge of Ras-immunized mice with syngeneic tumor cells expressing mutant Ras oncoproteins (HaBalb, i.e., BALB/c mouse cells expressing Ras with arginine substituted at amino acid position 12 [Arg 12 Ras]; C3HL61, i.e., C3H/HeJ mouse cells expressing Ras with leucine substituted at position 61 [Leu 61 Ras]). Ten mice per group were used in each experiment. **RESULTS:** Proliferative and cytolytic T-cell responses directed against the Arg 12 Ras protein were generated in BALB/c mice, resulting in protection against challenge with

cells expressing Arg 12 Ras and therapeutic benefit in mice bearing established tumors expressing this protein. In C3H/HeJ mice, high levels of cytolytic and proliferative responses were induced against Leu 61 Ras. Immunization with heat-killed *E. coli* genetically engineered to express Leu 61 Ras also led to the induction of anti-Ras T-cell immunity. T cells grown under TH1 conditions were cytolytic against Ras-transformed tumor cells, whereas those grown under TH2 conditions were not. **CONCLUSIONS:** Immunization as described here leads to Ras mutation-specific antitumor immunity in vitro and in vivo, with therapeutic efficacy in an established tumor model.

MeSH

[Animal](#) ; [Cytokines](#) ; [Cytotoxicity, Immunologic](#) ; [Escherichia coli](#) ; [Immunity, Cellular](#) ; [Lymphocyte Transformation](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Mice, Inbred C3H](#) ; [Neoplasms, Experimental](#) ; [Peptides](#) ; [Point Mutation](#) ; [Proto-Oncogene Protein p21\(ras\)](#) ; [Recombinant Proteins](#) ; [T-Lymphocytes, Cytotoxic](#) ; [T-Lymphocytes, Helper-Inducer](#) ; [Vaccination](#) ;

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Features of oral immunization.

[Ruedl C](#), [Wolf H](#)

Int Arch Allergy Immunol 1995 Dec **108**:4 334-9

Abstract

In this review, we focus on some key areas concerning the unique properties of the mucosal immune system. They are: (1) the fact that the common mucosal immune system consists of different compartments; (2) the advantages of oral vaccination, which can be exploited to antigen-specific sIgA-mediated local immune responses as well as systemic immunity; (3) efficacious oral immunization against respiratory infections; (4) oral tolerance with respect to activation of T cells which, after declining, can be repeatedly reinduced without changes in profile or magnitude, and (5) the use of transgenic plants as a new vaccine source for a new vaccination strategy, i.e. employing edible dietary vaccines.

MeSH

[Administration, Oral](#) ; [Animal](#) ; [Bacterial Infections](#) ; [Bacterial Vaccines](#) ; [Human](#) ; [IgA, Secretory](#) ; [Immunity, Mucosal](#) ; [Immunization](#) ; [Mouth Mucosa](#) ; [Plants, Transgenic](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Vaccination](#) ;

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B7-1 and B7-2 costimulatory molecules activate differentially the Th1/Th2 developmental pathways: application to autoimmune disease therapy.

[Kuchroo VK](#), [Das MP](#), [Brown JA](#), [Ranger AM](#), [Zamvil SS](#), [Sobel RA](#), [Weiner HL](#), [Nabavi N](#), [Glimcher LH](#)

Cell 1995 Mar 10 **80**:5 707-18

Abstract

CD4 T helper precursor cells mature along two alternative pathways, Th1 and Th2. Here we show that these pathways

are differentially activated by two costimulatory molecules, B7-1 and B7-2. Using anti-B7 antibodies, this developmental step was manipulated both in vitro and in vivo in experimental allergic encephalomyelitis (EAE). Anti-B7-1 reduced the incidence of disease while anti-B7-2 increased disease severity. Neither antibody affected overall T cell induction but rather altered cytokine profile. Administration of anti-B7-1 at immunization resulted in predominant generation of Th2 clones whose transfer both prevented induction of EAE and abrogated established disease. Since co-treatment with anti-IL-4 antibody prevented disease amelioration, costimulatory molecules may directly affect initial cytokine secretion. Thus, interaction of B7-1 and B7-2 with shared counterreceptors CD28 and CTLA-4 results in very different outcomes in clinical disease by influencing commitment of precursors to a Th1 or Th2 lineage.

MeSH

[Amino Acid Sequence](#) ; [Animal](#) ; [Antibodies, Monoclonal](#) ; [Antigens, CD80](#) ; [Cell Differentiation](#) ; [Cells, Cultured](#) ; [Encephalomyelitis, Allergic](#) ; [Female](#) ; [Immunotherapy, Adoptive](#) ; [Interferon Type II](#) ; [Interleukin-4](#) ; [Lymph Nodes](#) ; [Membrane Glycoproteins](#) ; [Mice](#) ; [Mice, Transgenic](#) ; [Molecular Sequence Data](#) ; [Myelin Basic Proteins](#) ; [Proteolipids](#) ; [Support, Non-U.S. Gov't](#) ; [Support, U.S. Gov't, P.H.S.](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Vaccination](#) ;

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Immunity to *Schistosoma mansoni* in mice vaccinated with irradiated cercariae: cytokine interactions in the pulmonary protective response.

[Smythies LE](#), [Coulson PS](#), [Wilson RA](#)

Ann Trop Med Parasitol 1993 Dec **87**:6 653-7

Abstract

In C57BL/6 strain mice vaccinated with attenuated cercariae of *Schistosoma mansoni*, the major site of immune elimination of challenge parasites is the lungs. We have monitored pulmonary events after both vaccination and challenge by bronchoalveolar lavage, and examined the profile of cytokines released by recovered cells upon stimulation with larval antigens in vitro. From 14 days post-vaccination, lavage samples contain infiltrating lymphocytes which produce abundant interferon-gamma (IFN-gamma) and interleukin-3 (IL-3). We suggest that the lymphocytes recruited to the lungs are effector/memory cells of the Th1 subset. Challenge of vaccinated mice results in a second influx of IFN-gamma- and IL-3-secreting cells into the airways, earlier than after vaccination alone, or in appropriate controls. Ablation studies reveal that CD4+ T cells are the source of the IFN-gamma. The timing of cytokine production after both vaccination and challenge coincides with phases of macrophage activation already recorded, and with the presence of parasites in the lungs. Administration of monoclonal antibody directed against IFN-gamma, over the period of challenge elimination, almost completely abrogates protection in vaccinated mice, but does not affect the ratio of Th1:Th2 cells in the lungs. Immunity in this model is not, however, affected by inhibition of nitric oxide production, or neutralization of TNF. We suggest that the effector mechanism may operate by blocking parasite migration, and that loss of protection following neutralization of IFN-gamma may be attributed to changes in composition, density and cohesiveness of pulmonary foci.

MeSH

[Animal](#) ; [Antigens, Helminth](#) ; [Interferon Type II](#) ; [Interleukin-3](#) ; [Lung](#) ; [Mice](#) ; [Mice, Inbred C57BL](#) ; [Schistosoma mansoni](#) ; [Support, Non-U.S. Gov't](#) ; [T-Lymphocytes](#) ; [Time Factors](#) ; [Vaccines](#) ; [Vaccines, Attenuated](#) ;

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 [J Neuropathol Exp Neurol](#)

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Prevention of experimental autoimmune neuritis by nasal administration of P2 protein peptide 57-81.

[Zhu J](#), [Deng GM](#), [Levi M](#), [Wahren B](#), [Diab A](#), [van der Meide PH](#), [Link H](#)

J Neuropathol Exp Neurol 1998 Mar **57:3** 291-301

Abstract

Experimental autoimmune neuritis (EAN) is a CD4+ T cell-mediated inflammatory demyelinating disease of the peripheral nervous system (PNS) that serves as a model for Guillain-Barre syndrome (GBS) in humans. Both EAN and GBS are associated with upregulated T and B cell responses to PNS myelin proteins including P2 protein, and by changes of the Th1/Th2 cell balance in favor of Th1. Here we report that EAN can be prevented by the dominant neurotoxic peptide 57-81 of the PNS P2 protein when given nasally before immunization of Lewis rats with bovine PNS myelin (BPM) + Freund's complete adjuvant (FCA). P2 peptide-tolerized rats were also resistant to EAN relapse after challenge with BPM. Tolerance to EAN in rats receiving high dose (60 microg/day/rat) P2 peptide nasally was associated with specific T and B cell anergy. This was characterized by the failure of T cells to proliferate in response to PNS myelin antigens, while responsiveness to phytohemagglutinin was retained. Numbers of BPM- and P2 peptide-reactive interferon-gamma mRNA expressing lymph node cells were reduced, while levels of P2 peptide-reactive interleukin 4 and transforming growth factor-beta mRNA-expressing cells were markedly upregulated on day 18 post immunization in the rats receiving high dose P2 peptide nasally. Tolerance to EAN was also associated with lower CD4+ cell infiltration, low-grade inflammation, or the absence of histological evidence of EAN, as well as with low IL-2 receptor and MHC class II molecule expression within the PNS. This is the first study showing that mucosal tolerance is applicable to EAN and, as an extension, could be considered in GBS.


MeSH

[Administration, Intranasal](#) ; [Animal](#) ; [B-Lymphocytes](#) ; [Cattle](#) ; [Cell Count](#) ; [Cytokines](#) ; [Immunity, Mucosal](#) ; [Immunohistochemistry](#) ; [Lymphocyte Transformation](#) ; [Male](#) ; [Myelin P2 Protein](#) ; [Neuritis, Experimental Allergic](#) ; [Peptide Fragments](#) ; [Rats](#) ; [Rats, Inbred Lew](#) ; [RNA, Messenger](#) ; [Sciatic Nerve](#) ; [Support, Non-U.S. Gov't](#) ; [T-Lymphocytes](#) ; [Vaccination](#) ;

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Development of immune functions related to allergic mechanisms in young children.

[Koning H](#), [Baert MR](#), [Oranje AP](#), [Savelkoul HF](#), [Neijens HJ](#)

Pediatr Res 1996 Sep **40:3** 363-75

Abstract

The newborn immune system differs quantitatively and functionally from that of adults. Development of the immune system has important implications for childhood diseases. The immaturity of the immune system in the first years of life may contribute to failure of tolerance induction and in the development of allergic disease. T cell function is diminished, especially the capacity to produce cytokines; production of interferon (IFN)-gamma, and IL-4 is strongly reduced. IFN-gamma has been found to be even lower in cord blood of newborns with a family history of atopy. Differences in other cell types (natural killer cells, antigen-presenting cells, and B cells) could also play a role in the development of allergic disease. Current data suggest that irregularities in IgE synthesis, helper T cell subsets (Th1, Th2, CD45RA, and CD45RO), cytokines (IL-4, IFN-gamma), and possibly other cell types may play a role in the development of allergy in childhood. Moreover, the role of cell surface molecules, like co-stimulatory molecules (CD28, CD40L), activation markers (CD25), and adhesion molecules (LFA-1/ICAM-1, VLA-4/VCAM-1) is also discussed. These variables are modulated by genetic (relevant loci are identified on chromosome 5q, 11q, and 14) and environmental forces (allergen exposure, viral infections, and smoke). The low sensitivity of current predictive factors for the development of allergic diseases, such as cord blood IgE levels, improves in combination with family history and by measurement of in vitro responses of lymphocytes and skin reactivity to allergens. New therapeutic approaches are being considered on the basis of our current understanding of the immunopathology of allergic disease, for instance cytokine therapy and vaccination with tolerizing doses of allergen or peptides.

MeSH

[Child](#) ; [Child, Preschool](#) ; [Environmental Health](#) ; [Human](#) ; [Hypersensitivity](#) ; [Immune System](#) ; [Immunization](#) ; [Infant](#) ; [Infant, Newborn](#) ; [Predictive Value of Tests](#) ; [Risk Factors](#) ;

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Relationship between Th1/Th2 cytokine patterns and the arthritogenic response in collagen-induced arthritis.

[Mauri C](#), [Williams RO](#), [Walmsley M](#), [Feldmann M](#)

Eur J Immunol 1996 Jul 26:7 1511-8

Abstract

It is hypothesized that the balance of cytokines produced by Th1/Th2 subsets of T helper cells plays an important role in the development of autoimmune diseases. Murine collagen-induced arthritis (CIA) is an example of an autoimmune disease in which immunization with cartilage-derived type II collagen induces, firstly, a T cell response to type II collagen and, secondly, the manifestation of a destructive inflammatory response in affected joints. We have investigated the role of Th1/Th2 responses in the development of CIA by monitoring levels of interferon (IFN)-gamma (a Th1 cytokine) and interleukin (IL)-4 and IL-10 (Th2 cytokines), and IL-1 beta and tumor necrosis factor (TNF) (pro-inflammatory cytokines) produced by cultured draining lymph node cells (LNC) from collagen-immunized DBA/1 mice during the induction phase of arthritis and throughout the time of clinical manifestation and subsequent remission of the disease. Although a transient increase in IL-10 was detected 3 days after immunization, Th2 cytokine production was found to be almost completely suppressed 6 days after immunization. In contrast, IFN-gamma was detected in LNC cultures as early as 6 days after immunization and the addition of type II collagen to the culture medium resulted in an approximately 10-fold increase in IFN-gamma production, indicating that a predominantly Th1 response had become established by this time. IFN-gamma production by LNC was found to be further increased at the time of clinical manifestation of arthritis and could be up-regulated by co-culture with type II collagen. IL-10 was not detected in LNC cultures at the onset of arthritis and IL-4, although present, was found to be markedly suppressed in LNC cultures containing type II collagen. These findings indicate that Th1 responses are predominant at the time of onset of arthritis and that the activation of collagen-specific Th1 cells may result in suppression of Th2 activity. IFN-gamma production declined progressively during the progression and subsequent remission of arthritis whereas levels of IL-10 increased and low, though persistent, levels of IL-4 were detected throughout this period. High levels of IL-1 beta and TNF-alpha production were detected at the onset of the disease. The role of Th1 responses in the development of CIA was further emphasized by the observation that immunization of mice with type II collagen in incomplete Freund's adjuvant, which normally fails to induce arthritis, resulted in a predominantly Th2 cytokine profile.

MeSH

[Animal](#) ; [Arthritis, Adjuvant](#) ; [Collagen](#) ; [Cytokines](#) ; [Freund's Adjuvant](#) ; [Interleukin-1](#) ; [Kinetics](#) ; [Lymph Nodes](#) ; [Lymphocyte Transformation](#) ; [Male](#) ; [Mice](#) ; [Mice, Inbred DBA](#) ; [Remission Induction](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Tumor Necrosis Factor](#) ;

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Th1/Th2 cell dichotomy in acquired immunity to Bordetella pertussis: variables in the in vivo priming and in vitro cytokine detection techniques affect the classification of T-cell subsets as Th1, Th2 or Th0.

[Barnard A](#), [Mahon BP](#), [Watkins J](#), [Redhead K](#), [Mills KH](#)

Immunology 1996 Mar 87:3 372-80

Abstract

In studies of the mechanism of immunity to *Bordetella pertussis* in a murine respiratory infection model, we have previously demonstrated that natural infection of immunization with a whole cell vaccine induces a potent protective immune response, which is mediated by T-helper type-1 (Th1) cells. In contrast an acellular vaccine generates Th2 cells and is associated with delayed bacterial clearance following respiratory challenge. In the present study we have investigated the apparent Th1/Th2 cell dichotomy in acquired immunity and have examined the factors that affect their induction or detection. The cytokine profiles of *B. pertussis*-specific T cells in immune animals were determined using antigen-stimulated ex vivo spleen cells or CD4+ T-cell lines and clones established in the presence of interleukin-2 (IL-2) or IL-4. Antigen-specific T cells derived from mice immunized with the acellular vaccine were almost exclusively of the Th2 cell type. In contrast, T-cell lines and clones established following respiratory infection or immunization with the whole cell vaccine were predominantly of the Th1 type. However, a proportion of T cells from convalescent mice, especially when cultured in the presence of IL-4, secreted IL-4 and IL-5 with or without detectable IL-2 and interferon-gamma (IFN-gamma), suggesting that Th0 or Th2 cells were also primed during natural infection in vivo. Furthermore, when mice were assessed 6 months after infection, spleen cells produced significant levels of IL-4 and IL-5, which were not evident at 6 weeks. The route of immunization and the genetic background of the mice were also found to influence the preferential priming of Th1 cells, and this was directly related to the level of protection against respiratory or intracerebral (i.c.) challenge. Our findings underline the critical role of CD4+ Th1 cells in immunity to *B. pertussis*, but also demonstrate that a number of factors in the in vivo priming and in vitro restimulation can skew the apparent dominance of one Th cell type over another.

MeSH

[Animal](#) ; [Bordetella pertussis](#) ; [Cytokines](#) ; [CD4-Positive T-Lymphocytes](#) ; [Immunity, Cellular](#) ; [Immunization](#) ; [Interferon Type II](#) ; [Interleukin-2](#) ; [Interleukin-4](#) ; [Mice](#) ; [Mice, Inbred BALB C](#) ; [Mice, Inbred CBA](#) ; [Support, Non-U.S. Gov't](#) ; [Th1 Cells](#) ; [Th2 Cells](#) ; [Whooping Cough](#) ;

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