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OPŠTI PREGLED

GENERAL REVIEWS

Imuni mehannizmi posredovani Th-17 celijskim i IL-23 odgovorom: postoji li regulacija putem PGE2-oslobađajućih makrofaga u BCG -imunizovanih miševa? Pregled literature i krajnji dometi

Th-17 CELL IL-23 PATHWAY - mediated immune responses : is there a regulation by PGE2-releasing macrophages in BCG-immunized mice? Literature review and up-date

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APSTRAKT

U ovom pregledu, pod autoimunim oboljenjima, uključujući i neke oblike ateroskleroze, smatraju se kompleksne interakcije citokina koje u datom miljeu održavaju i obnavljaju napade inflamatornih reakcija poznatih kao„flare“. Bazični mehanizam koji omogućava ovakav milje je disbalans veoma kompleksnog Th1/Th2 imunog odgovora. Naša grupa je pokazala u dosadašnjim radovima da injekcija Mycobacterium bovis bacillus Calmette-Guérin (HK-BCG) mišu dovodi do pojave različitih populacija makrofaga (Mϕ) koji ili oslobadjaju ili ne oslobadjaju prostaglandin 2 (PGE2) te zavisno od toga mogu doprineti promociji ili inhibiciji inflamatornog procesa, disbalansu u odnosu Th1/Th2 imunih ćelija i konačno, razvoju autoimunog oboljenja.

Produkcija PGE2 aktiviranih makrofaga je pojačana tokom inflamacije, kada ovaj lipidni medijator može dramatično da modulira imuni odgovor mada je jos nepoznato, kako? Stoga postoji potreba za razjašnjenjem njegove modulatorne uloge u kompleksnom citokinskom miljeu (posredovanom ćelijama),u razvoju infalamatornih i autoimunih oboljenja. Jedno od njih je atroskleroza, široko rasprostranjen, fatalni sindrom oboljenja koja se prostiru u spektru od inflamatornih do autoimunih manifestacija u ljudi i mišjih modela. Poslednjih godina, postalo je očigledno da IL-12, STAT4 i IFN-γ , i stoga Th1 ćelije, nisu primarni kreatori modela inflamatornih oboljenja. Pre će biti da su patogene ćelije u ovim modelima indukovane u odgovoru na signale proizvedene in vivo IL-12-sličnim citokinom IL-23, a karakterišu se produkcijom niza citokina, hemokina, efektornih molekula i transkripcionih faktora koje ih razlikuju od spektra indukovanog

ABSTRACT

In this review autoimmune disease (AD), included atherosclerosis is considered in part result of the complex cytokine interactions of different cell types in the body and maintenance of perpetuation of inflammatory attacks known as „flares“. The statement that Th1/Th2 disbalance with either Th1 or Th2 dominance reflects the complexity and uniqueness of each particular immunological scenario is underlined. The work of our group have demonstrated that injection of Mycobacterium bovis bacillus Calmette-Guérin (HK-BCG) results in the distinct COX-2 macrophage (M ϕ) populations which do or do not release PGE2 and may contribute functionally to inhibition or promotion of inflammation, Th1/Th2 shift, and/or development of autoimmune disease (AD).

The production of PGE2 from activated Mϕ is enhanced during inflammation, when this lipid mediator can dramatically modulate immune response although it is not known how. Therefore, there is a need for clarification of its regulatory role in a complex cell-mediated and cytokine milieu within the spectrum of inflammatory and autoimmune diseases. One of them is atherosclerosis, widespread, fatal syndrome ranging from inflammatory to autoimmune background in both: mouse and humans. During the past few years, it has become apparent that IL-12, STAT4 and IFN-γ , and therefore Th1 cells, are not the primary instigators of model inflammatory diseases. Rather, the pathogenic cells in these models of disease are induced in response to signals provided in vivo by the IL-12-like cytokine IL-23, and are characterized by the production of a suite of cytokines, chemokines, effector molecules and transcription factors distinct from that of

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Th1 ćelijama. Jedan od najeksprimiranijih gena u ovim efektornim ćelijama je gen koji kodira pro-inflamatorni citokin IL-17.

Još specifičnije, PGE2 – zavisna akvizicija T regulatorne (T reg) ćelijske funkcije koreliše sa indukcijom FOXP3 gena i ekspresijom kodiranog proteina. Pojačana inhibitorna aktivnost PGE2-tretiranih CD4+CD25+ T reg ćelija takodje je praćena značajnom „ up-regulacijom" FOXP3. Ovo saopštenje osvetljava nove moguće uloge PGE2 molekula u kontroli generacije i funkcije T reg ćelija.

Nedavno je demonstrirana i na genetskom nivou potvrdjena polarizacija Mϕ. S druge strane, kliničke studije su pokazale visoku korelaciju izmedju infekcije mikobakterijom i ateroscleroze, dok su mišji modeli aterogeneze utvrdjeni (postavljeni) korišćenjem HK-BCG. Stoga, HK-BCG aktivirani Mϕ slezine predstavljaju trenutno glavni cilj za razumevanje mehanizama dejstva njihovih prostanoidnih sekretornih produkata u razlicitim modelima inflamacije i autoimunih oboljenja, uključujući ateroskleroza uzrokovanom inflamacijom vezanom za infektivne agense kao što je HK-BCG. Da li u spektru aterosklerotičnih oboljenja Th—17,IL-23 put vezan za produkciju prostaglandina iz Mϕ ima ulogu, i do koje mere, ostalo je da se utvrdi.

Ključne reči:
Ateroskleroza, HK-BCG, T-17 ćelije, IL-23, PgE2-oslobađjajući makrofazi

Th1 cells . One of the genes most highly expressed in these effector cells is the pro-inflammatory cytokine IL-17.

More specific, the PGE2 – dependent acquisition of T regulatory (Treg) cell function was correlated with induction of FOXP3 gene and its coding protein expression. The enhanced inhibiting activity of PGE2-treated CD4+CD25+ T reg cells was also associated with significant up-regulation of FOXP3. This report highlights novel roles for PGE2 in controlling the generation and function of Treg cells.

Quite recently, polarization of Mϕ has been demonstrated and confirmed at a genetic level. On the other hand, clinical studies have shown high correlation between mycobacterial infection and atherosclerosis, while mouse models of atherogenesis were established by using HK-BCG. Therefore, HK-BCG activated splenic Mϕ are current target for understanding mechanisms of action of their prostanoid secretory products in different models of inflammation and AD, including atherosclerosis caused by inflammation linked to infectious agents, especially HK-BCG.

Key words:
Atherosclerosis, HK-BCG, T-17 cells, IL-23, PgE2-releasing macrophages

INTRODUCTION: BACKGROUND AND SIGNIFICANCE

The work of our group have demonstrated that injection of *Mycobacterium bovis* bacillus Calmette-Guérin (HK-BCG) results in the distinct COX-2 macrophage populations which do or do not release PGE_2 and may contribute functionally to inhibition or promotion of inflammation, Th1/Th2 shift, and/or development of autoimmune disease (AD)(1–6). Fenton's group have shown that both virulent and attenuated strains of *M. tuberculosis* could activate the cells in a TLR-dependent manner (TLR2 and TLR4 pathways). Cytokines have also been shown to play a crucial, albeit complex regulatory role in control of inflammation and autoimmunity. Because of their pleiotropic effect and redundancy, it is unlikely that one single cytokine can be the key determinant in the occurrence of immune disorders, but it may act as a booster. AD is in part result of the complex cytokine interactions on different cell types in the body and maintenance of perpetuation of inflammatory attacks known as „flares". Th1/Th2 disbalance with either Th1 or Th2 dominance reflects the complexity and uniqueness of each particular immunological scenario. Th1 responses mediated usually via IL-2 and IL-12 are implicated in some inflammatory and AD, such as ulcerative colitis (UC) and systemic lupus erythematosus (SLE), while Th2 responses via IL-4 are likely to contribute to allergy, atopy and asthma. Some AD are both Th1 and Th2 mediated. (Fig.1.)

In fact, IL-2, IFN-α, IFN-β, IFN-γ, and TNF-α, can either enhance or limit inflammatory and/or autoimmune processes. The production of PGE_2 from activated macrophages is enhanced during inflammation, when this lipid mediator can dramatically modulate immune response although it is not known how? (7). Therefore, there is a need for clarification of its regulatory role in a complex cell-mediated and cytokine milieu within the spectrum of inflammatory and autoimmune diseases. One of them is atherosclerosis, widespread, fatal syndrome ranging according to experimental and clinical data from inflammatory to autoimmune background in both: mouse and humans (1–3). Our previous results on mouse model of atherosclerosis in BCG immunized mice have demonstrated dose-dependent inflammation and calcification of aortic wall (1–4).

STATE OF THE ART:

- PGE_2 releasing macrophages in HK-BCG induced WT mouse model of inflammation: Role of Th-17 - IL-23 pathway in chronic inflammation and AD

The results of our studies suggest that after 1 day of 1 mg i. p. injected HK-BCG, following phagocytosis of intracellular bacteria, local (peritoneal) Mϕ express catalytically inactive COX-2, without PGE_2 secretion. This may enhance macrophage-mediated innate and Th1 acquired immune response against intracellular infections sensitive to endogenous PGE_2. On the other hand, after 7 and 14 days following such injection, activated local Mϕ expressed induced COX-2 activity with consecutive release of PGE_2 which may be relevant in particular locations and at particular concentrations. The Th17 cells, a newly discovered distinct lineage of proinflammatory T helper cells, are now considered essential for inflammation and AD in both: mice and humans (8) (Fig.2.)

In mice, commitment to the T h-17 lineage is dependent on transforming growth factor-β (TNF-β) and interleukin 6 (IL-6) (8–10).These cells produce the proinflammatory cytokine IL-17, responsible for the recruitment, proliferation and activation of granulocytes in an inflammatory setting. The newly discovered, IL-23 *(9)* secreted by activated macrophages and DC, supports a distinct lineage of Th-17 cells (producing IL-17) by binding to the **I**L-23 receptor on the surface of Th17 cells and mediating chronic inflammation, as it is defined in chronic colitis in mice, and in Reumathoid Arthritis (RA), Autoimmune Bowel Disease (IBD) and Diabetes type1 in humans. (9) However, IL-17 has been also implicated in the pathogenesis of several AD, such as EAE (experimental autoimmune encephalitis) and CIA (collagenase induced arthritis), the mouse models of Multiple Sclerosis (MS) and Rheumatoid Arthritis (RA) respectively. Both IL-12 and IL-23 bind to receptors from the same family: heterodimers with a unique and shared subunit p40. During the past few years, it has become apparent that IL-12, STAT4 and IFN-, and therefore Th1 cells, are not the primary instigators of model inflammatory diseases(12). Rather, the pathogenic cells in these models of disease are induced in response to signals provided *in vivo* by the IL-12-like cytokine IL-23, and are characterized by the production of a suite of cytokines, chemokines, effector molecules and transcription factors distinct from that of Th1 cells (11–15). One of the genes most highly expressed in these effector cells is the pro-inflammatory cytokine IL-17. Additional features of Th17 cells include the production of IL-22 and expression of IL-23R. These IL-17-producing $CD4^+$ T cells have been recognized as key mediators of inflammation and tissue damage in several animal models of human diseases. Following the characterization of Th17 cells, interest turned to identifying the factors responsible for their generation. IL-23 was initially proposed as a key mediator of Th17-cell generation, because IL-23-deficient mice displayed severely decreased numbers of IL-17 producing $CD4^+$ T cells compared to wild-type mice. Later work, however, revealed that IL-23 was not required for the generation of Th17 cells from naïve T cells *per se*, but rather acted later on cells that were already committed to the Th17 lineage. (9–11).This was consistent with the original finding that IL-23 promoted proliferation of activated/memory, but not resting/naïve $CD4^+$ T cells. (13) Subsequently, it was shown that IL-17 production by naïve $CD4^+$ T cells could be driven by TGF- and IL-6. These cytokines act in a STAT3-dependent manner to induce expression of the orphan nuclear receptor ROR t, which subsequently increases production of IL-17. Thus, analogous to the central roles played by T-bet and GATA3 in generating Th1 and Th2 cells, respectively, ROR t is considered to be the transcription factor responsible for guiding the development of Th17 cells. The role of TGF- in the development of these cells is particularly interesting, as TGF- is also important for driving the generation of regulatory T cells. Thus, TGF- will promote the differentiation of inhibitory Treg. However, in the presence of additional inflammatory signals such as IL-6, Th17 cells will be generated. Thus, IL-6 represents a crucial switch for controlling the differentiation of $CD4^+$ T cells to the Th17 or Treg lineages. (Fig.3.)

It remained unclear, though, whether other cytokines were also capable of controlling this switch.

Recent studies from the Kuchroo, Dong, Littman and other labs approached this question from different perspectives, but all reached the same conclusion that IL-21, a member of the IL-2 family of cytokines, also controls the generation of Th17 cells.(18–21). They showed that IL-21, in combination with TGF-, induces IL-17 production from naïve $CD4^+$ T cells. This was accompanied by the acquired expression of RORγ t and IL-23R. Conversely, IL-21 inhibited the generation of $FoxP3^+$ Treg induced by TGF-. Furthermore, analysis of IL-6-deficient mice revealed that the ability of IL-21 to generate Th17 cells from $CD4^+$ T cells was independent of IL-6. Thus, IL-21, like IL-6, can dictate the generation of Th17 versus Treg. For both IL-21 and IL-6, this switch seems to be mediated by STAT3 and ROR t. These papers also demonstrated that IL-6 or IL-21 could induce Th17 cells themselves to produce IL-21 (autocrine loop). Such endogenous production of IL-21 by Th17 cells appeared to be biologically significant, because the number of IL-17-producing cells generated by TGF- and IL-6 was reduced in the absence of IL-21/IL-21R signalling. Thus, IL-6 can elicit IL-21 production by $CD4^+$ T cells, which then functions in an

autocrine loop to amplify the Th17 response in a similar way to IL-4 for Th2 and IFN- for Th1 cells. Furthermore, both IL-21 and IL-6 upregulated IL-23R, thereby priming Th17 cells to the amplifying and stabilizing effects of IL-23.

Targeting molecules involved in the generation, maintenance and effector function of Th17 cells, such as TGF-, IL-6, IL-23 and IL-17, have been proposed as novel therapeutics for human inflammatory disorders. These findings on the role of IL-21 in the biology of Th17 cells add IL-21 to this list of potential targets. In particular, since IL-21 functions in a self-amplifying loop on established Th17 cells, IL-21 may be a better target for inhibiting the pathogenic inflammatory response than IL-6. Recent reports showing that neutralizing IL-21 in murine models of lupus or rheumatoid arthritis ameliorated disease severity demonstrate the potential utility of IL-21-targeted therapies for human autoimmune conditions (18–21).

These findings also raise some interesting questions that will no doubt be addressed in future studies. First, Th17 cells are not the only population of $CD4^+$ T cells capable of producing IL-21. Indeed, $CXCR5^+$ T follicular helper (T_{FH}) cells are also a rich source of this cytokine. Interestingly, T_{FH} cells have also been found to be overrepresented, and assumed to be disease-causing, in murine lupus. Humans deficient in ICOS have a reduction in the frequency of circulating T_{FH} cells, and activated $CD4^+$ T cells from these patients exhibit reduced production of IL-17. (20) The reduction in IL-17 secretion may be a direct result of the deficiency of circulating T_{FH} cells in ICOS-deficient patients. Thus, it is tempting to speculate that T_{FH} cells are also capable of producing IL-17. For these reasons, in addition to the finding that both T_{FH} and Th17 cells can provide B-cell help for Ab production, it will be important to establish the relationship between Th17 cells and T_{FH} cells to determine whether they have a common developmental programme. It will also be important to determine whether production of IL-21 by T_{FH} cells contributes to the generation of Th17 cells, or whether the IL-21 required for this process is strictly derived in an autocrine manner.

Second, it will be important to determine if other signature Th17 mediators, such as IL-22, are differentially regulated by IL-6 and IL-21 and whether the abilities of both IL-6 and IL-21 to induce Th17 cells represent redundant systems, or if they favour the development of Th17 cells for responses against specific pathogens. For instance, it has been found that animal models of inflammatory dermatitis can develop independently of IL-17 and that production of IL-17 and IL-22 by Th17 cells is differentially regulated in such conditions. Thus, it is possible that Th17 cells induced by TGF- and either IL-6 or IL-21 make qualitatively different contributions to the development of inflammation depending on the pathogen and affected tissue. Notwithstanding these uncertainties, these recent findings expand our understanding of Th17 cells and highlight potential new strategies for effectively treating human inflammatory diseases.

- PGE_2 receptors on hematopoietic and non-hematopoietic cells: their significance for inflammation and AD

PGE_2, is an important mediator of the immune response, including the recruitment of bone marrow precursor cells through CXCR4/SDF-1 (CXCL12) system and the shift from Th1 to Th2 dominant responses (1 - 6). The exact role of a specific prostanoid in the inflammatory response is often ambiguous. There are 4 already cloned and sequenced receptors for PGE_2 (EP1-EP4) with unique patterns of expression and different coupling to intracellular signaling pathways in different cells of immune system (11). So, by acting on different subtype receptors on different cells in the body, prostaglandins can exert opposing pro- or anti-inflammatory effects. For example, activation of D prostanoid 1 receptor *suppresses* asthma by modulation of lung dendritic cell (DC) function and induction of regulatory T-cells (T-reg) (12). It is considered that EP2 receptors directly inhibit T- cell proliferation, while EP2 and EP4 receptors together regulate antigen presenting and different cell functions in DC *(11)*. It seems that prostaglandins can enhance or suppress both inflammation and/or perpetuation of flares in AD by acting on different receptors expressed by Treg cells. It has been shown that immature dendritic cells (iDC) have EP1, EP2, and EP4 receptors. (11). The induction of IL-23 is mediated through PGE2 which binds to EP2 and possibly, EP4 receptors. The results (11) indicate that PGE_2 induces the early expression of both IL-23 subunits, with no significant effect on P35, and therefore on IL-2 expression (11–16). PGE2 induces p19, p40 but not p35 expression in dice. So, PGE2 induces resident iDC to generate IL-23 which in turn induces IL-17, a potent proinflammatory cytokine secreted by activated T-cells and synovial cells. It is also found in synovial fluid of RA patients. These known facts raise the question: what is the exact mechanism of PGE_2 releasing macrophages in BCG-immunized mice in regulation of TH-17 cell mediated immune response? If DC have prostaglandin receptors and bind the ligand with consecutive IL-23 subunit expression and IL-17 induction in the lymph nodes, skin, and beneath the linings of GIT, do macrophages in the spleen have similar or different pattern of regulation? How does that pattern look like in HK-BCG immunized mice?

- PGE_2 releasing macrophages in aorta and spleen of mice treated with i. p. injection of HK-BCG

The spleen is the lymphoid tissue where PGE_2 Mϕ and immune lymphocytes interact in chronic inflammatory diseases. PGE_2 inhibits production of Th1 cytokines (IL-2, IL-12, and INF-γ . In contrast, PGE_2 on depending stimulatory conditions has no effect or enhances production of Th2 cytokines (IL-4, IL-5, and IL-10). (1) The development of Th1 cells against HSP65 from BCG mediates resistance to *Mycobacterium tuberculosis* which constitutes major vaccine strategy against TBC. However, the results of the work of our group strongly suggest that in recurrent or chronic infections, anti HSP65 which does not have a decisive, protective role against *mycobacterium* infection, may promote the further progression of disease development, for example of atherosclerotic plaques in atherosclerosis(1–4). Our very recent data performed on cells isolated from wild type (Wt) mouse aorta and spleen have confirmed strong signal for COX-2 activity on Western Blot and stimulation of PGE_2 secretion by both HK-BCG and calcium ionophore A 23187, suggesting macrophage activation in these localities 7 days after i. p. injection of 1 mg of HK-BCG and inflammation of aortic wall.

- PGE_2 induced FoxP3 gene expression in (CD4+CD25+ Treg) cells: their function in human CD4+ T cells

Human FOXP3 is a crucial regulatory gene for the development and function of CD4+CD25+ regulatory T cells and can be used as their reliable marker. Transcription factor FOXP3 conversion of CD4+CD25 Naïve T cells to CD4+CD25 Tregs (TGF-β induced) is described as a step involved in Treg cell differentiation. It was also confirmed that prostaglandin E2 induced FOXP3 gene expression and T reg cell function in human CD4+ T cells (l3). This was the first report indicating that PGE_2 can modulate FOXP3 expression and Treg function in human lymphocytes. Their importance resides in their pivotal role in the maintenance of immunological tolerance. Barabelli et al, further hypothesized that PGE_2 secreted by tumor associated macrophages (TAM) could contribute to tumor-induced immunosupression through modulation of Treg cell function. More specific, the PGE_2 – dependent acquisition of Treg cell function was correlated with induction of FOXP3 gene and its coding protein expression (13). The enhanced inhibiting activity of PGE_2-treated CD4+CD25+ T reg cells was also associated with significant up-regulation of FOXP3 (13). This report highlights novel roles for PGE_2 in controlling the generation and function of Treg cells. Summary on the role of Th1,Th2, Th17 and Treg cells is given in Table 1. , and is self-explanatory.

- Polarization of Mϕ and /or DC as a prerequisite for T-cell polarization (differentiation))through cross talk between Mϕ-and T cells and/or DC and T-cells

The fate of T-cell mediated immune response is dependent on the preceding polarization of primarily Mϕ and/or DC, which will through the action upon naïve and consequently regulatory T-cells finally polarize the pool of T-cells, into Th1, Th2 and Th17-leading to proper balance or disbalance (named Th1/Th2 or Th2/Th1 shift), with implications for eventual immunotherapy. Exposure to pathogens triggers the maturation of DC, a multistep process whereby DC sequentially induce innate and adaptive responses against invading pathogens. Initially, DC secrete cytokines and chemokines that recruit innate effector cells, such as neutrophils and Mϕ to the site of infection; these cells exert potent antimicrobial activities, and keep the pathogen in check. Subsequently, the maturing DC (mDC) migrate to draining lymph nodes, where they activate and expand antigen-specific T- cells, effectors of adaptive immunity. Activated T-cells migrate back to the site of inflammation, clear the infection and give rise to the memory response. Clearly, pathogen recognition by DC is a crucial process in the host defense against infectious agents. Once in the lymph nodes, immature DC (iDC) present self-antigens to autoreactive T-cells that escaped thymic selection, resulting in the deletion of the autoreactive T-cells or the induction of T-regs. Therefore, DC orchestrate T-cell responses against self and non-self by eliciting immunity in response to a pathogen challenge and establishing peripheral tolerance in the steady state. Quite recently, polarization of Mϕ has been demonstrated and confirmed at a genetic level (17). On the other hand, clinical studies have shown high correlation between mycobacterial infection and atherosclerosis, while mouse models of atherogenesis was established by using HK-BCG. Therefore, HK-BCG activated splenic Mϕ are current target for understanding mechanisms of action of their prostanoid secretory products in different models of inflammation and AD, including atherosclerosis caused by inflammation linked to infectious agents, especially HK-BCG. Whether the Th-17 IL-23 pathway and PGE_2 producing Mϕ have the role in at least some section of the spectrum of this disease, is to be confirmed in future studies.

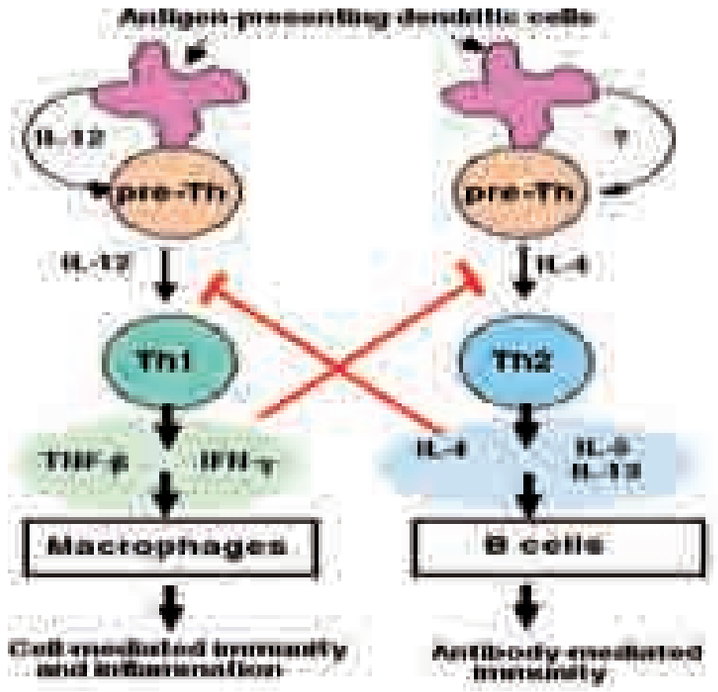
Antigen-presenting dendritic cells
IL-12
pre-Th
pre-Th
IL-12
IL-4
Th1
Th2
TNF-β
IFN-γ
IL-4
IL-5
IL-13
Macrophages
B cells
Cell-mediated immunity and inflammation
Antibody-mediated immunity

Fig.1
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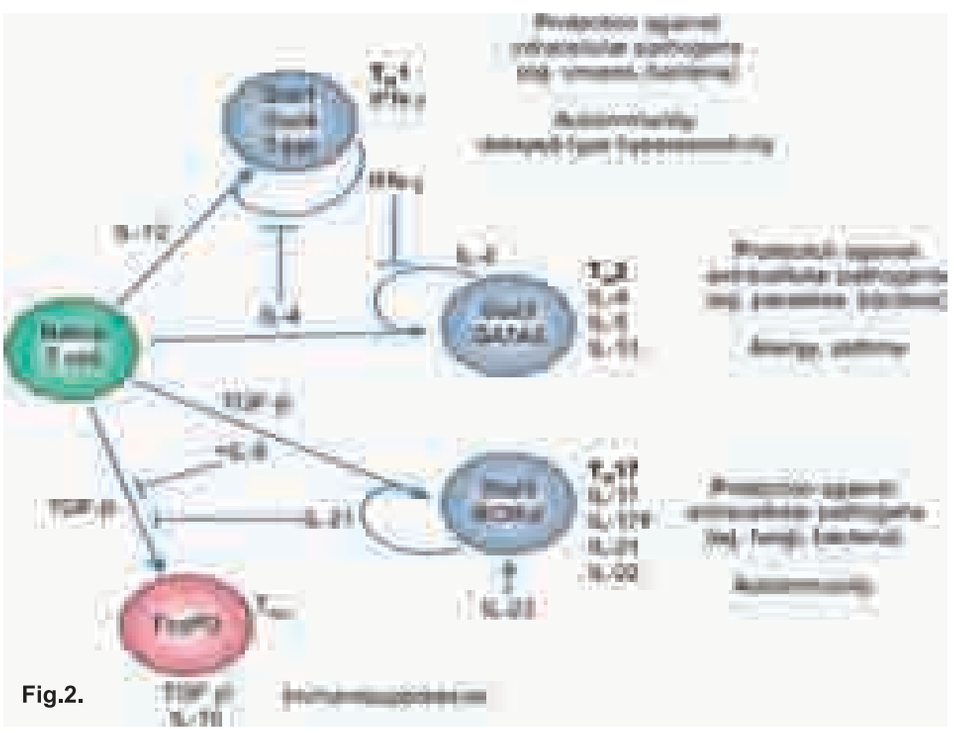

Fig.2.

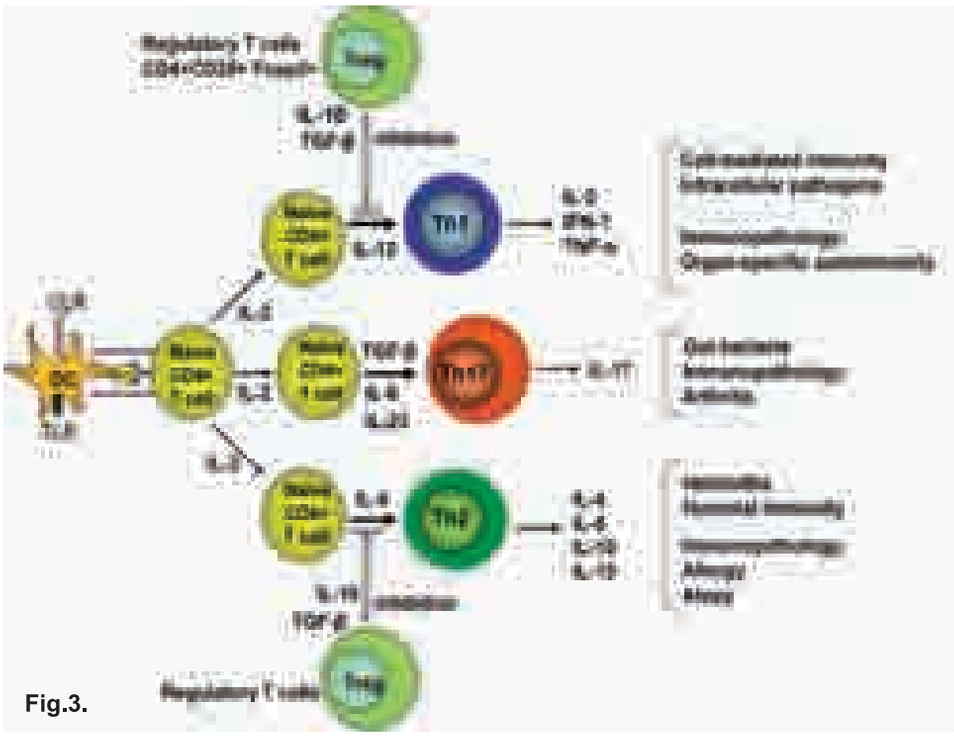

Fig.3.

Summary Table 1.

Type	Cytokine Stimulus	Master Transcription Factor	Effector Cytokine(s)	Effector Functions	Pathological Effects
Th1	IL-12	T-bet	IFN-γ	Intracellular pathogens	Autoimmunity; cell-mediated allergies
Th2	IL-4	GATA-3	IL-4	Extracellular pathogens	Asthma and IgE-mediated allergies
Th17	TGF-β plus IL-6 Inhibited by retinoic acid	RORγ	IL-17 & IL-22	Extracellular bacteria; mediates inflammation	Autoimmune diseases
Treg	TGF-β minus IL-6 Stimulated by retinoic acid	Foxp3	TGF-β	Immunosuppression; anti-inflammatory	None?

REFERENCES:

1. Shibata Y. et al: Splenic PGE-2 releasing macrophages regulate Th1 and Th2 immune responses in mice treated with HK-BCG. .*Journal of Lukocy Biology*,2005,78, pp.1281–1290
2. Shibata Y, Honda, I: A Th1-adjuvant –N-acetyl-D-glucosamine polymer up-regulates Th-1 immunity but down-regulates Th-2 immunity against a mycobacterial protein (MPB-59) in IL-10 knockout and wild type mice. *Infect Immunol*. 69, 6123–6130
3. Shibata Y., Volkman A.1985 The effect of bone marrow depletion on prostaglandind E producing supressor macrophages in mouse spleen. J Immunol.135, 3897–3904
4. Shibata Y(1989) Restauration of prostaglandin E2-producing splenic macrophages in 89 Sr-treated mice with bone marrow from Corynebacterium parvum –primed donors. *Reg. Immunol.*2,169–175
5. *Yamashita M, Shinohara T, Tsuji S, Myrvik,QN, Nishiyama, A, Henriksen RA. and Shibata Y.* Catalytically Inactive Cyclooxygenase 2 and Absence of Prostaglandin E_2 Biosynthesis in Murine Peritoneal Macrophages following In Vivo Phagocytosis of Heat-Killed Mycobacterium bovis Bacillus Calmette-Guérin. *The Journal of Immunology*, 2007, 179: 7072–7078.
6. Yamashita M., Tsuji S, Nishiyama A, Myrvik QN, Henriksen RA and Shibata Y. Differential subcellular localization of COX-2 in macrophages phagocytosing heat-killed *Mycobacterium bovis* BCG. AJP: *Cell Physiology*, Manuscript ID: C-00346–2006.R
7. Nataraj et al., Thomas DV, Tilley SL, Ngyjen MT, Mannon R, Koller BH, and Coffman TM. 2001. Receptors for prostaglandin E2 that regulate cellular immune responses in the mouse. *J Clin Invest*.108:1229–1235
8. Wilson NJ, Boniface K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD, Basham B, Smith K, Chen T, Morel F, Lecron J-C, Kastelein RA, Cua DJ, McClanahan TK, Bowman EP, de Waal Malefyt R. Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol*. 2007 Aug 5; : 17676044
9. Elson CO, Cong Y , Weaver CT, Schoeb TR, McClanahan TK, Fick RB, Kastelein RA. Monoclonal Anti-Interleukin 23 Reverses Active Colitis in a T Cell-Mediated Model in Mice. *Gastroenterology.* 2007 Jun;132 (7):2359–2370 17570211
10. Veldhoen, M; Hocking, RJ; Atkins, CJ; Locksley, RM and Stockinger, B (2006) TGFß in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. *Immunity* 24,179-89
11. Sheibanie AF, Tadmori I, Jing H, Vassiliou E, Ganea D (2004). Prostaglandin E2 induces IL-23 production in bone marrow-derived dendritic cells. FASEB J 18:1318–132
12. Hammad H, Kool M, Soullie T, Narumiya S, Trottein F, Hoogsteden HC, Lambrecht BN. 2007. Activation of the D prostanoid 1 receptor supresses asthma by modulation of lung dendritic cell function and induction of T regulatory cells. JEM, 204,2:357–367
13. Baratelli F, Lin Y, Yang SC, Heuze-Vourch N, Zeng G, Reckamp K, Dohadwala M, Sharma S.,Dubinett SM.2005. Prostaglandin E2 induces FOXP3 Expression and T Regulatory Cell Function in Human CD4+ T cells. *The Journal of Immunology*, 175:1483–1490
14. Chackerian A A, Chen S-J, Brodie SJ, Mattson JM, McClanahan TK, Kastelein RA, Bowman EP. Neutralization or absence of the IL-23 pathway does not compromise immunity to mycobacterial infection. *Infect Immun*. 2006 Aug 21; : 16923792
15. Chan JR, Blumenschein W, Murphy E, Diveu C, Wiekowski M, Abbondanzo S, Lucian L, Geissler R, Brodie S, Kimball AB, Gorman DM, Smith K, de Waal Malefyt R, Kastelein RA, McClanahan TK, Bowman EP. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. *Exp Med.* 2006 Oct 30; : 17074928
16. Verreck FA, de Boer T, Langenberg DM, Hoeve MA, Kramer M, Vaisberg E, Kastelein R, Kolk A, de Waal-Malefyt R, Sttenhoff TH (2004) Human IL-23-producing type1 macrophages promote but IL-10-producing type2 macrophages subvert immunity to (myco) bacteria. *Proc Natl Acad Sci* USA 101:4560–4565
17. Martinez FO, Sica A, Mantovani A, Locati M.2008. Macrophage activation and polarization. Frontiers in Bioscience 13, 453–461
18. Betelli E, Oukka M Kuchroo V, T_H-17 cells in the circle of immunity and autoimmunity. *Nature Immunology 8, 345 - 350 (2007)* doi:10.1038/ni0407–345
19. Korn T, Bettelli E, Gao W, Awasthi A, Jager A, Strom TB et al. IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. *Nature* 2007; 448: 484–487. |
20. Nurieva R, Yang XO, Martinez G, Zhang Y, Panopoulos AD, Ma L et al. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. *Nature* 2007; 448: 480–483.
21. Zhou L, Ivanov II, Spolski R, Min R, Shenderov K, Egawa T et al. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. *Nat Immunol* 2007; doi:10.1038/ni1488.

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