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Selective stimulation of T helper 2 cytokine responses by the anti-psoriasis agent monomethylfumarate

Type 2 cytokines are thought to have a protective role in psoriasis vulgaris by dampening the activity of T helper 1 (Th1) lymphocytes. The aim of the present study was to determine the effect of monomethylfumarate (MMF), the most active metabolite of the new anti-psoriatic drug Fumaderm®, on the production of cytokines and the development of Th subsets. MMF was found to enhance interleukin (IL)-4 and IL-5 production by CD2/CD8 monoclonal antibody-stimulated peripheral blood mononuclear cells (PBMC) in a dose-dependent manner. Maximal effects of MMF were found at a concentration of 200 μM and resulted in tenfold enhanced levels of IL-4 and IL-5 production. MMF did not affect the levels of IL-2 production, interferon (IFN)-γ production or proliferative T cell responses in these cultures. Similar effects of MMF were observed in cultures of purified peripheral blood T cells indicating that this compound can act directly on T cells. MMF did not influence cytokine production by purified $CD4^+CD45RA^+$ (unprimed) T cells, but greatly enhanced IL-4 and IL-5 production without affecting IFN-γ production by purified $CD4^+CD45R0^+$ (primed) T cells. Furthermore, MMF also augmented IL-4 and IL-5 production in established Th1/Th0 clones that were stimulated with CD2/CD28 monoclonal antibody. Finally, when PBMC were challenged with *Mycobacterium tuberculosis* that typically induces Th1 recall responses with strong IFN-γ secretion, MMF again appeared to induce high levels of IL-4 and IL-5 secretion while IFN-γ production was unaffected. These results may be relevant for the development of therapeutic regimens designed to correct inappropriate Th1 subset development in immunopathologic conditions.

1 Introduction

$CD4^+$ T helper (Th) cells can be classified in at least three subsets according to their functional program. Th1 cells typically secrete high amounts of IL-2 and IFN-γ whereas Th2 cells are characterized by their ability to produce high levels of IL-4 and IL-5 upon activation [1, 2]. Th cells with shared features of Th1 and Th2 cells are referred to as Th0 cells [2]. Protective immunity towards intracellular pathogens such as *Listeria monocytogenes, Leishmania major* and *Mycobacterium* species depends on a Th1 response, while Th2 cells promote disease [3, 4]. In several models of organ-specific autoimmune diseases, on the other hand, Th1 responses promote disease development whereas Th2 responses are associated with disease resistance [5–7]. The most important factors that control Th cell differentiation are IL-12 and IL-4 that drive Th1 and Th2 cell development, respectively [3, 8, 9]. The products of Th1 and Th2 cells have a negative regulatory effect on the growth and function of the opposing subset, which may lead to a reinforcement of polarizing differentiation events, particularly in chronic responses [10, 11].

Psoriasis vulgaris is characterized by epidermal hyperplasia with cellular infiltrates of lymphocytes and monocytes [12]. Psoriasis is presumed to be a Th1-associated autoimmune disease based on a preferential isolation of Th1 cells from psoriatic skin lesions [13, 14]. Moreover, IFN-γ could be localized in suction blister fluid from psoriatic lesions [15] and significantly higher levels of IFN-γ were found in the serum of psoriasis patients than in the serum of healthy controls [16]. Clinical efficacy of cyclosporin A, CD4 mAb and IL-2 toxin in psoriasis treatment has been well established [12, 17, 18]. In addition, clinical improvement in psoriasis vulgaris and psoriatic arthritis patients has also been observed upon therapy with Fumaderm® [19–22]. Fumaderm® is composed of monoethylfumarate (MEF) and dimethylfumarate (DMF). The most effective fumarate metabolite of this drug is monomethylfumarate (MMF), which is formed in the circulation by hydrolysis of DMF [23]; (personal communication Dr. R. K. Joshi, ETH Dept. of Pharmacy, Zürich, Switzerland). Considering the possibility that these compounds may act in psoriasis by modulating Th1/Th2 subset development, we analyzed the ability of MMF to redirect T cell cytokine secretion profiles. Our data indicate that MMF is able selectively to up-regulate the secretion of cytokines that are associated with type 2 immune responses.

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Abbreviations: DMF: Dimethylfumarate **MEF:** Monoethylfumarate **MMF:** Monomethylfumarate

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2 Materials and methods

2.1 Reagents

mAb directed against CD2 (CLB-T11.1/1, CLB-T11.2/1 and CLB-CD2 clone HIK27, all IgG1), CD28 (CLB-CD28/1, IgG1), CD3 (CLB-T3/4.E, IgE), CD8 (CLB-T8/4), CD19 (CLB-CD19), CD14 (CLB-CD14) and CD16 (CLB-FcR-gran1) were produced at the Central Laboratory of the Red Cross Blood Transfusion Service (CLB), Amsterdam, The Netherlands. CD45RA (2H4) mAb was purchased from Coulter Immunology (Hialeah, FL). CD45R0 mAb was generously provided by Dr. P. Beverly (University College, London, GB). MMF (Fumapharm AG, Muri, Switzerland) was prepared as a stock solution of 10 mM in PBS; the pH was adjusted to 7.2 with 0.1 N NaOH. The stock was stored at 4° and diluted appropiately before use. Purified protein derivative (PPD) of *Mycobacterium tuberculosis* was obtained from Statens Seruminstitute, Copenhagen, Denmark.

2.2 T cells

Peripheral blood was obtained from buffy coats of healthy blood bank donors. PBMC were isolated from heparinized blood by Ficoll-Amidotrizoate density centrifugation. Purified peripheral blood T cells were isolated after rosette formation with aminoethylisothiouronium bromide hydrobromide-treated sheep red blood cells followed by Ficoll-Amidotrizoate centrifugation. After lysis of sheep red blood cells, T cell fractions consisting of > 98 % $CD2^+$ cells were obtained. For the experiments on CD45R subsets, lymphocytes were isolated from PBMC by counterflow centrifugation elutriation. $CD4^+$ T cell subsets were subsequently prepared by negative magnetic bead immunoselection. Cells were incubated for 45 min at 4 °C with saturating amounts of CD8, CD14, CD19, CD16 and CD45RA or CD45R0 mAb. After two washes, sheep anti-mouse Ig-coated magnetic beads were added (Dynabeads M450, Dynal A.S., Oslo, Norway). After a 60-min incubation at 4 °C, rosetted cells were removed with a Dynal magnetic particle concentrator. The negatively selected fractions were > 97 % $CD4^+$, < 2 % $CD8^+$ and did not contain detectable levels of CD14-expressing cells. The resulting purity for CD45R0 and CD45RA antigen expression was > 93 % and 95 %, respectively. The $CD4^+$ T cell clones that were used in this study are specific for *Mycobacterium leprae* and represent Th1 or Th0 type clones [24, 25].

2.3 Detection of binding sites for methylated fumarates

Investigation of the presence of binding sites for methylated fumarates was performed as described [26] with minor modifications. Briefly, approximately 1×10^6 purified T cells (> 98 % $CD2^+$)/100 µl RPMI 1640 supplemented with 20 mM Hepes (pH 7.4) and 10 mg BSA/ml were incubated with 49 µM [^{14}C] DMF (specific activity 8.1 Ci/mol, Hazleton, Harrogate, GB; a kind gift from Dr. R. K. Joshi) and various concentrations of unlabeled MMF or DMF. After 90 min at 0 °C, 1 ml cold RPMI 1640 supplemented with 20 mM Hepes pH 7.4 and 10 mg/ml BSA/ml was added and the cells were centrifuged at 160 × g for 10 min. After washing twice, the cells were transferred for scintillation counting. From these data, the concentration of MMF causing 50 % inhibition (ID_{50}) of the binding of [^{14}C] DMF to T cells was calculated. The specific activity of the radiolabeled methylated fumarates available is not high enough to perform calculations on the number of binding sites per T cell and the binding affinity of these sites for MMF.

2.4 T cell stimulation

PBMC were plated at 7.5×10^5 cells/ml, purified peripheral blood T cells at 5×10^5 cells/ml and $CD4^+$ T cell clones at 10^6 cells/ml in 96-well plates (200 µl/well). Culture medium consisted of Iscove's Modified Dulbecco's medium (IMDM, Gibco BRL, Scotland) supplemented with 10 % FCS and antibiotics. Triplicate cultures of T cells were stimulated with a triplet of CD2 mAb (CLB-T11.1/1, CLB-T11.2/1 and CLB-CD2 clone HIK27) and CD28 mAb (CLB-CD28/1). In some experiments, a combination of CD28 mAb and CD3 mAb (CLB-T3/4.E) was used for stimulation. The mAb were used at a concentration of 5 µg/ml and have been previously described to induce high levels of cytokine secretion [27, 28]. Cells cultured in medium alone were included as negative controls. MMF was added at the initiation of the cultures in concentrations ranging from 50–400 µM. Culture supernatants were collected at 24 h to measure IL-2 secretion and at 72 h to quantitate IL-4, IL-5 and IFN-γ production. These intervals were found to be optimal for the induction of the respective cytokines by T cells.

For induction of recall antigen responses to *M. tuberculosis*, PBMC were stimulated with 5 µg/ml PPD either in the presence or absence of MMF. After 6 days, 20 U/ml rIL-2 (Eurocetus, Amsterdam, The Netherlands) was added. At day 13, cells were washed and restimulated (7.5×10^5 cells/ml) with CD2 mAb and CD28 mAb. Supernatants were harvested for cytokine analysis 3 days later.

2.5 T cell proliferation assay

In parallel with the cultures that were set up for the measurement of cytokine secretion, T cells were plated for the analysis of proliferative responses. On day 4, 0.5 µCi [^{3}H] thymidine ([^{3}H] dThd) (6.7 Ci/mmol, Du Pont de Nemours Nederland B.C., Dordrecht, The Netherlands) was added to each well. After a 16-h pulse, incorporation was determined by liquid scintillation counting. Proliferation is expressed as mean cpm of triplicate cultures. The SD between the triplicates was < 10 %.

2.6 Cytokine measurements

IL-2 production was analyzed by bioassay using the IL-2-dependent CTLL-2 line [29]. Half-maximal proliferation in CTLL cells is induced with 1 U/ml rIL-2 (Eurocetus). IL-4, IL-5 and IFN-γ production were assayed by ELISA. For detection of IL-4, flat-bottom microtiter plates (Maxisorb, Nunc, Roskilde, Denmark) were coated overnight using CLB-IL4/5 (CLB, Amsterdam, The Netherlands) [28]. Following incubation with serial dilutions of culture

supernatants and rIL-4 as standard, biotinylated CLB-IL4/1 (CLB) was added as a secondary mAb. Thereafter, plates were washed and incubated with horseradish peroxidase-conjugated streptavidin (Pierce, Rockford, IL) for 30 min washed and developed with 100 μg/ml 3,5,3′,5′-tetramethylbenzidine (Merck, Darmstadt, Germany), 0.003 % H_2O_2 in 0.11 M sodium acetate pH 5.5. The reaction was stopped by addition of 50 μl of 2 M H_2SO_4/well. Plates were read at 450 nm in a Titertek microplate reader. ELISA for the other cytokines were performed in a similar manner. IL-5 production was determined using TRFK5 mAb as a primary mAb and biotinylated JES1-5A10 mAb as capture antibody (both from Pharmingen, San Diego, CA). For detection of IFN-γ, plates were coated with 4SB3 mAb (European Collection of Animal Cell Cultures) and biotinylated MD-1 mAb was used as a secondary anti-IFN-γ mAb [30]. One U/ml IFN-γ was equal to 23 pg/ml. The detection level of the assays is 0.5 U/ml for IL-2, 60 pg/ml for IL-4, 0.5 ng/ml for IL-5 and 100 U/ml for IFN-γ.

3 Results

3.1 Effects of MMF on lymphocyte proliferation and cytokine production

The presence of binding sites for MMF on purified T cells was inferred from the ability of both unlabeled MMF and DMF to compete equally well with [^{14}C] DMF for binding to peripheral blood T cells in a dose-dependent manner ($ID_{50} \sim 6$ mM MMF). To study the functional effects of MMF on T lymphocytes, a first series of experiments were performed in which PBMC were stimulated with a combination of CD2 mAb and CD28 mAb in the presence of titrated amounts of MMF. MMF in concentrations ≤200 μM did not affect proliferative responses. Since 400 μM MMF largely inhibited T cell proliferation (Fig. 1A), in line with toxic concentrations of MMF for phagocytes and keratinocytes [23, 31], all further experiments were performed in concentrations of MMF ranging from 50–200 μM. MMF stimulated both IL-4 and IL-5 production by activated T cells in a dose-dependent manner (Fig. 1D and E). Maximal effects were obtained using a concentration of 200 μM MMF and resulted in tenfold increased levels of both IL-4 and IL-5 production. Neither IL-2 nor IFN-γ production was modulated by MMF (Fig. 1B and C). Similar findings were obtained when CD3 mAb instead of CD2 mAb were used for stimulation (data not shown). MMF by itself did not stimulate the release of these cytokines (Table 1 and 2).

3.2 Kinetics of IL-4 and IL-5 release in the presence of MMF

The levels of IL-4 and IL-5 secretion in the presence of MMF were analyzed at different time points after T cell stimulation. PBMC were stimulated with CD2/CD28 mAb in the presence of 100 μM and 200 μM MMF. MMF caused an increase in the levels of IL-4 and IL-5 production within 2 days after T cell activation (Fig. 2). The enhancing effects of MMF became more evident at later time points and lasted throughout the 5- day culture period (Fig. 2). Peak levels in IL-4 were reached at day 3–4 and the highest levels in IL-5 at day 5.

3.3 Regulatory effects of MMF on purified peripheral blood T cells

We examined whether MMF can also affect T cell cytokine production in the absence of accessory cells. For this pur-

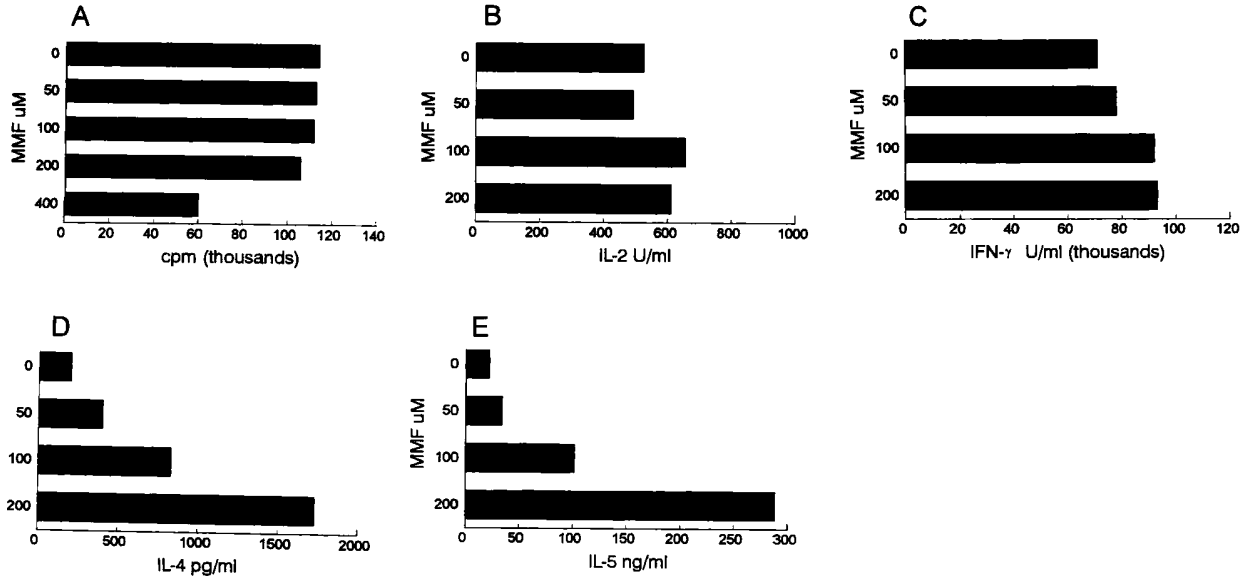

Figure 1. MMF enhances IL-4 and IL-5 but not IL-2 and IFN-γ production in PBMC. PBMC (7.5×10^5/ml) were stimulated with CD2 mAb (CLB-T11.1/1, CLB-T11.2/1 and CLB-CD2 clone HIK27) in combination with CD28 mAb (CLB-CD28/1). MMF was included at the indicated concentrations. Proliferative responses ([^{3}H] dThd incorporation; in cpm) were assayed at day 5. Supernatants were harvested from parallel cultures 24 h after stimulation for detection of IL-2, or 72 h after stimulation for the measurement of IFN-γ, IL-4 and IL-5 secretion. Nonstimulated cultures contained undetectable levels of cytokines and incorporated < 200 cpm. The given data are representative for one out of three experiments.

pose, purified T cells were isolated from PBMC by E-rosette sedimentation. In line with the results on PBMC, about tenfold increased levels of IL-4 production were measured when purified T cells were stimulated in the presence of 200 μM MMF (Table 1). MMF also enhanced IL-5 production in CD2/CD28 mAb stimulated T cells, although less vigorously than in PBMC (stimulation indices two- to threefold versus tenfold in PBMC, Table 1). Again, MMF did not induce cytokine secretion in unstimulated cultures. Comparable results were obtained when T cells were stimulated with either two or three distinct CD2 mAb in combination with CD28 mAb or when T cells were stimulated with CD3 mAb in combination with CD28 mAb (Table 1). MMF did not influence the magnitude of T cell proliferative responses (Table 1).

3.4 MMF enhances IL-4 and IL-5 production in $CD4^+CD45R0^+$, but not in $CD4^+CD45RA^+$ T cells

In peripheral blood, unprimed and primed $CD4^+$ T cells can be discriminated on the basis of expression of CD45RA and CD45R0 membrane molecules, respectively [32]. Functionally, these two subpopulations can be distinguished in that $CD4^+CD45R0^+$ (primed) T cells are the main producers of IL-4, IL-5 and IFN-γ upon T cell stimulation *in vitro* [32, 33]. We studied whether MMF modulates cytokine secretion by $CD4^+CD45R0^+$ T cells by $CD4^+CD45RA^+$ T cells, or both. As shown in Fig. 3, addition of MMF to CD2/CD28 mAb stimulated $CD4^+CD45R0^+$ T cells led to increased levels of IL-4 (mean enhancement 2.5-fold, $n = 3$) and IL-5 (mean

Table 1. Regulatory effects of MMF on purified peripheral blood T cells

Readout[c]	Stimulation[a]	MMF[b]			
		–	50 μM	100 μM	200 μM
Proliferation (cpm × 10^{-3})	Medium	0.3	0.2	0.3	0.3
	CD2 mAb (double) + CD28 mAb	69	77	79	80
	CD2 mAb (triple) + CD28 mAb	87	91	91	90
	CD3 mAb + CD28 mAb	71	80	79	77
IL-4 production (pg/ml)	Medium	< 60	< 60	< 60	< 60
	CD2 mAb (double) + CD28 mAb	458	940	1912	3546
	CD2 mAb (triple) + CD28 mAb	514	1026	1960	3302
	CD3 mAb + CD28 mAb	184	682	818	2960
IL-5 production (ng/ml)	Medium	< 1	< 1	< 1	< 1
	CD2 mAb (double) + CD28 mAb	194	334	454	563
	CD2 mAb (triple) + CD28 mAb	142	249	280	390
	CD3 mAb + CD28 mAb	313	474	493	586

a) Purified T cells (5×10^5/ml) were stimulated with either two CD2 mAb (CLB-T11.1/1 and CLB-T11.2/1) or three distinct CD2 mAb (CLB-T11.1/1, CLB-T11.2/1 and CLB-CD2 clone HIK27) in combination with CD28 mAb (CLB-CD28/1). Alternatively, cells were stimulated with CD3 mAb (CLB-T3/4.E) in combination with CD28 mAb (CLB-CD28/1). Unstimulated cells were included as a control.
b) MMF was added at the initiation of the culture in concentrations as indicated.
c) T cell proliferation was assayed by [^{3}H] thymidine incorporation; IL-4 and IL-5 production was assayed by ELISA.

Table 2. IL-4 and IL-5 production by $CD4^+$ T cell clones in the presence of MMF

T cell clone[a]	MMF μM[b]	IL-4 pg/ml		IL-5 ng/ml	
		Medium	CD2/28	Medium	CD2/28
SCII-1G6	0	< 60[c]	120	1[c]	76
	100	< 60	450	2	91
	200	< 60	600	1	90
SCVIII-2D3	0	< 60	60	< 1	18
	100	< 60	160	< 1	28
	200	< 60	320	< 1	51
SCVIII-2D6	0	< 60	60	1	32
	100	< 60	280	< 1	65
	200	< 60	520	< 1	80
R1F9	0	< 60	60	nt[d]	62
	100	< 60	120	nt	99
	200	< 60	280	nt	104
SCIX-1F6	0	nt	160	< 1	40
	100	< 60	440	< 1	48
	200	< 60	840	< 1	44
SCI-1G2	0	nt	960	< 1	396
	100	< 60	1320	< 1	368
	200	< 60	1400	< 1	516

a) $CD4^+$ T cell clones were cultured for 3 days with medium or CD2 mAb and CD28 mAb.
b) MMF was added at the initiation of the culture at the indicated concentration.
c) Data represent the mean cytokine contents of triplicate cultures measured by specific ELISA.
d) nt: not tested.

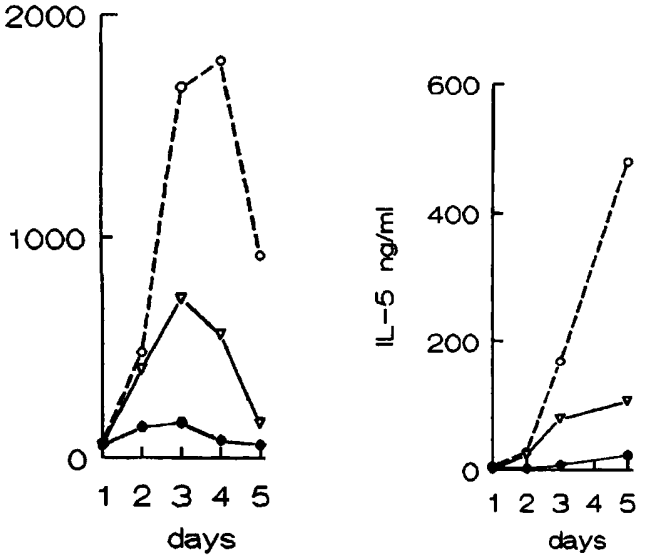

Figure 2. Kinetics of IL-4 and IL-5 production in PBMC stimulated with CD2/CD28 mAb and MMF. PBMC (7.5×10^5/ml) were stimulated with CD2/CD28 mAb in the absence (–●–) or presence of 100 μM (MMF (–▽–) and 200 μM MMF (–○–). Supernatants were assayed for IL-4 and IL-5 production by ELISA at the indicated time points after stimulation.

enhancement 3-fold, $n = 3$). MMF again did not affect the magnitude of the IFN-γ response (Fig. 3), nor did it induce detectable levels of any cytokine in the absence of T cell stimuli. As expected, $CD4^+CD45RA^+$ T cells secreted little or no IL-4 and IL-5 and only low levels of IFN-γ following stimulation with CD2/CD28 mAb. This cytokine secretion pattern was not modified by MMF (Fig. 3). These data show that MMF exerts its regulatory effects (mainly) on the $CD4^+CD45R0^+$ T cell population.

3.5 MMF influences cytokine secretion by Th1 $CD4^+$ T cell clones

The findings described above show the modulatory capacity of MMF to stimulate type 2 cytokines in polyclonal T cell populations of primed cells. Next, to investigate whether MMF is capable of modulating the T cell cytokine secretion profile of (virtually) fully differentiated cells away from their Th1 phenotype at the clonal level, we tested the modulatory effects of MMF on established $CD4^+$ Th1 clones that had frequently been stimulated with antigen over time. Th1 (low IL-4/low IL-5/high IFN-γ producers) $CD4^+$ T cell clones and a Th0 (high IL-4/high IL-5/high IFN-γ producer) $CD4^+$ T cell clone that we have described previously [24, 25] were activated with CD2/CD28 mAb in the absence or presence of MMF for 3 days. MMF enhanced IL-4 production in all $CD4^+$ T cell clones tested (mean enhancement about fivefold at 200 μM MMF, $n = 6$, Table 2). Enhanced levels of IL-5 secretion after addition of MMF were seen in five out of six clones (mean enhancement about twofold in these clones at 200 μM MMF) (Table 2).

3.6 MMF modulates T cell responses to recall antigen

Finally, to analyze the modulatory effects of MMF on recall antigen responses, representing physiologically integrated T cell/APC interactions, PBMC were stimulated with PPD of *Mycobacterium tuberculosis* in the presence or absence of 100 or 200 μM MMF. T cell blasts were expanded by adding 20 U/ml rIL-2 at day 6. At day 13, T cells were harvested, washed and restimulated with CD2/CD28 mAb for 3 days in the absence of MMF. CD2/CD28 mAb induced equally high levels of proliferation in all populations, showing that MMF had not affected the ability of T cells to proliferate as expected (Fig. 4). PPD has been documented to mount typically Th1 responses [24]. Indeed, the generation of antigen-specific T cells in the absence of MMF resulted in a population of T cells that secreted high levels of IFN-γ but little or no detectable IL-4 and IL-5 upon restimulation (Fig. 4). The antigen-specific T cells that were generated in the presence of MMF, in contrast, produced vast amounts of IL-4 and moderate quantities of IL-5 upon activation, while their ability to secrete IFN-γ was unaffected by the MMF treatment (Fig. 4.) These findings are in agreement with our above observations and indicate that MMF resets the Th subset balance during antigen-specific memory T cell responses.

4 Discussion

The present results demonstrate that the anti-psoriatic agent MMF can selectively up-regulate IL-4 and IL-5 secretion by human T cells. This modulatory effect of MMF was observed in cultures of PBMC, purified T cells, primed peripheral blood $CD4^+CD45R0^+$ T cells, recall responses to *M. tuberculosis* and, interestingly, even in

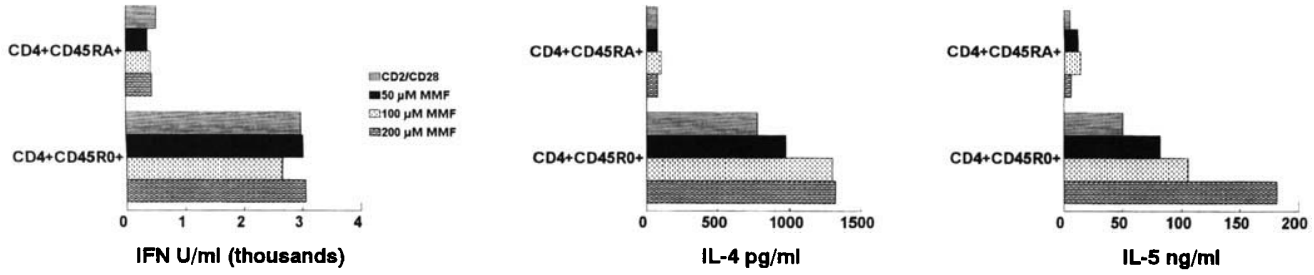

Figure 3. MMF increases IL-4 and IL-5 production in $CD4^+CD45R0^+$ T cells and not in $CD4^+CD45RA^+$ T cells. Purified T cell subsets (5×10^5 cells/ml) were stimulated with CD2/CD28 mAb for 3 days. Supernatants were assayed for their cytokine content by ELISA.

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