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Author
Woodley, Robin Maureen

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ELUCIDATION OF SUPPRESSOR CELL SUBSETS BY TARGET SPECIFICITY AND MARKER HETEROGENEITY

by

ROBIN MAUREEN WOODLEY

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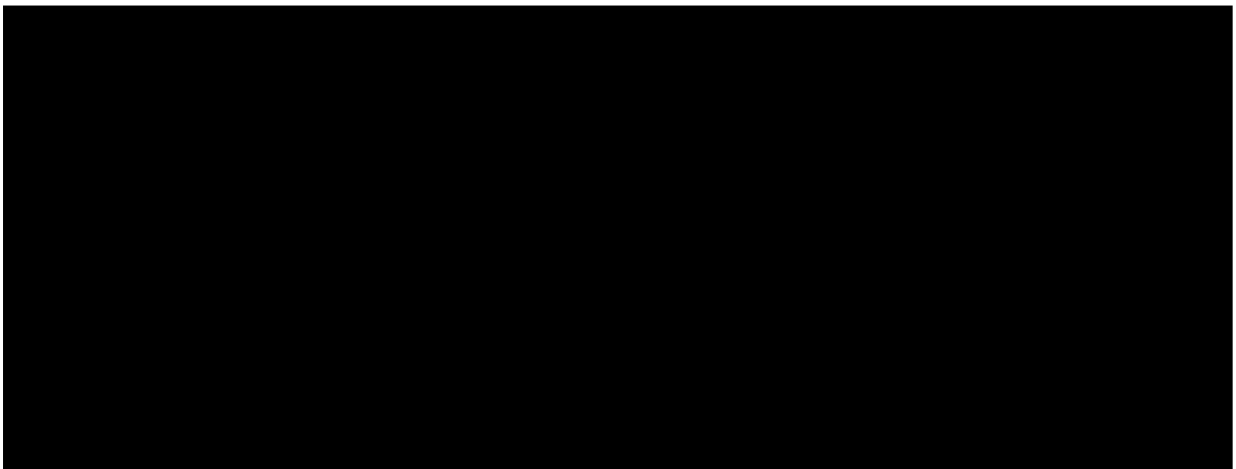

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ELUCIDATION OF SUPPRESSOR CELL SUBSETS BY TARGET SPECIFICITY AND MARKER HETEROGENEITY

CONTENTS

ABSTRACT

Heterogeneity exists in the T suppressor cell (Ts) population. This heterogeneity is defined by target specificity, radiosensitivity, and by cellular phenotypic markers. Most Ts cells have T helper (Th) cells as targets, however both monocytes/macrophages (MØ) and B cell targets have been described.

In these experiments, Ts induced by either ConA stimulation or alloantigenic stimulation of normal human peripheral blood mononuclear cells (PBMC) were assayed for their effect on monocyte production of the protease, plasminogen activator (PA). PA is a functional assay for facilitory MØ activity. Examination of Ts depression of PA production identified particular Ts subsets which have MØ as a direct target. Immunosuppression by ConA stimulated autologous PBMC's demonstrated that the PA producing MØ is the target of an OKT8(+) cell.

Depletion of OKT8(+) cells with monoclonal antibody and complement resulted in an average of 52% abrogation of suppression. Furthermore, positive selection of OKT8(+) cells with a FACS II cell sorter demonstrated significant enhancement of suppressive activity. These data suggest that an OKT8(+) cell directly mediates suppression of MØ functions. However, definite heterogeneity exists in the suppressive population. Significant suppression remained after OKT8(+) cell depletion, and the FACS sorted OKT8(-) population was also suppressive for MØ PA production. Addition of 1×10^{-6}M PGE 2 was not consistently effective in enhancing suppressor cell generation.

Initial experiments examining the effect of MLR generated suppressor cells indicated that MLR suppressor cells can suppress MØ PA production. However, the suppression was significantly less than that demonstrated by mitogenic induction of suppressor cells.

INTRODUCTION

Experimental models of suppressor activity in antigen induced, mitogen induced, and alloantigen (MLR) induced systems have been investigated [1] [2] [3]. Alterations in human T cell subsets in clinical disease suggest that perturbations of T helper cell to T suppressor cell ratios influence either the expression or the chronicity of many disease states [4] [5]. Different experimental models have suggested a variety of targets of suppressor cells [6] [7] [8]. These suppressive circuits may be similar, or may use different cells as suppressor effectors that act upon these targets (macrophage, T helper, or B cell).

Recent work in this laboratory has focused on the MØ as a target of suppression. Normal human peripheral blood monocytes spontaneously produce plasminogen activator, a monocyte specific protease functionally identifying monocyte/macrophage helper activity. Depressed monocyte plasminogen activator (PA) production has been correlated with the development of PHA hyporesponsiveness, and is an indicator of monocyte-T cell defective interactions [9].

The purpose of this work was the elucidation of the cell(s) responsible for facilitory MØ suppression, and the phenotypic marker(s) of the suppressive cells generated by mitogenic or alloantigenic stimulation. The focus of the work undertaken was to determine if the MØ is a target of Concanavalin A (ConA) and/or MLR generated suppressor cells, to identify the phenotype of the suppressor cell(s) by deletion and enhancement experiments, and to investigate the role of PGE 2 in suppressor cell generation.

I. Monocyte Production of PA as a Functional Assay

The multicellular interactions involved in immune responsiveness increase the desirability of a unicellular functional assay to detect targets of those interactions. Monocyte production of PA allows a focused examination of the effects of a variety of suppressor cells induced by both mitogens and alloantigens on the activity of the facilitory monocyte. Examination of different suppressive subpopulations identified by monoclonal antibody markers leads to a clearer understanding of specific cellular circuits and the ramifications of perturbations of selected subgroups.

II. Human Peripheral Blood Mononuclear Cells

Immune responses to particular antigens require orchestrated collaberation between many different subpopulations of leukocytes, including MØ, T helper cells, T inducer/amplifier cells, T suppressor cells, and B cells. Other subpopulations (killer cells, natural killer cells) may be involved in cellular modulation as well. Certain disease states involving immune dysfunction have been characterized by their responses to mitogenic stimulation, including leukemias, multiple sclerosis, systemic lupus erythematosus, and major trauma [10] [11] [12] [13]. Moreover, imbalances in subpopulations may be involved in the etiology and pathogenesis of autoimmune disease, common variable hypogammaglobulinemia, and multiple myeloma [14] [15] [16] [17] [18]. The response of human peripheral blood mononuclear cells to different mitogens has assumed a position of great clinical significance.

III. Concanavalin A Stimulation of Specific Subpopulations

The two most commonly studied T cell mitogens are ConA and PHA. Evidence that distinct T cell populations are stimulated has been provided by gradient fractionation [19] and cell surface markers [20].

ConA stimulates many subpopulations,and the concentration of ConA used profoundly affects the relative subpopulation stimulated. It has been suggested that the differences in stimulation of T helper (Th) and T suppressor (Ts) subpopulations by low or high doses of ConA is due to a difference in receptor density on the surface of the cells, with unstimulated Ts cells having a lower receptor density [21]. At optimum mitogenic doses, ConA stimulation often results in help rather than suppression, whereas in supraoptimal mitogenic concentrations, varying levels of suppression are seen. ConA generated suppressor cell activity has been investigated in systems involving antibody (PFC) [22], mitogenic restimulation (ConA, PHA) [23] and alloantigenic reactions (MLR) [24].

IV. Heterogeneity Within the Suppressor Cell Population

A prostaglandin mediated suppressor system has been well characterized by many investigators [25] [26]. Two additional categories of suppressor cells regulating T cell proliferation have been described [27]. There is a population of indomethicin resistant monocytic suppressor cells, and a population of non-adherent T cells produced as a result of an amplification of the suppressor T cell pool. All three types are mitogen inducible, steroid resistant, and not restricted by histocompatibility barriers. Alloantigenic stimulation induces an additional suppressor subset(s) that is histocompatibility (HLA-D) restricted [28] [29] [30].

Goodwin and his colleagues have conducted a series of experiments

characterizing the properties of the human PG producing suppressor cell [31] [32]. It is a glass adherent cell that suppresses T cell mitogenesis by secreting PGE 2. Removal of adherent cells eliminates enhancing effects of PG synthetase inhibitors in mitogen stimulated cultures to less than 10% normal.

Goodwin, Bankhurst, and Messner [33] also investigated the troublesome observation by Lomnitzer and Smith that abnormally high concentrations of PGE were required to suppress mitogen stimulation in cultures (5 micrograms/ml) compared to the amount of endogenous PG produced during mitogen stimulation (5 nanograms/ml). They were able to effect suppression in lower concentrations. In addition, they found that adding indomethicin to previously activated suppressor cells does not inhibit mitogen response via PG production.

Sakane and Green [34] used discontinuous (BSA) density gradient separation of T cells ConA stimulated populations. They concluded that ConA induced a population of high density (resting) T cells to develop suppressor function. These cells were characterized by a poor proliferative response to ConA. Low density (resting) T cells most capable of actively proliferating in response to ConA manifested no suppression.

The ConA stimulated Ts, but not ConA stimulated B cells, exerted suppressive influences on both B and T cell proliferative responses. Perhaps most importantly, Sakane and Green made specific note of heterogeneity among the suppressor cells generated. There appeared to be two distinct suppressors; one functioning as a suppressor for mitogenic responses of T cells (PHA, ConA), and another for mitogenic responses of

B cells (PWM) and the alloantigenic responses of T cells.

Classic studies by Mizerski et al on ConA induced suppressor cells in humans characterize the suppressor cell stimulated. Initial experiments [35] showed that the T enriched fraction of human PBMC contained the suppressive population. They provided indirect evidence that the ConA induced suppressor cells are radiosensitive T cells. Furthermore, as has been noted by most investigators, ConA induction of human mononuclear cells is dose and time dependent, and variable among individuals.

Additional work [36] further characterized cellular components of the ConA induction of suppression of allogeneic or autologous mitogenic responses. In the human system, MØ or the supernatants of MØ containing ConA stimulated cells are absolutely required for development of suppression. Furthermore, preincubation of adherent mononuclear cells with the suppressive supernatant rendered those cells suppressive. Supraoptimal mitogenic doses of ConA created a radiosensitive Ts cell inhibitory for mitogen responses. Additionally, after MØ dependent induction, an induced Ts cell produced a soluble suppressive substance (factor) which had the ability to bind to the surface of unstimulated MØ, which could then inhibit autologous mitogen responses. This suggested that a monocyte could become responsible for suppression of mitogenic responses by autologous lymphocytes. This inhibition could be abrogated by indomethicin.

The above cited work suggests the following cellular interactions: supraoptimal doses of ConA stimulate a MØ to elucidate a soluble factor acting on a modulating T cell. This modulating cell affects the development of a radiosensitive suppressor cell which also elucidates a

soluble factor (SIRS, MIF, SM, IFnII) [37] [38]. This factor may be picked up by an uninduced MØ or another unidentified cell involved in the effector phase of suppression.

The development of the radiosensitive T suppressor cell is linked to an indomethicin sensitive mechanism. The development of a MØ suppressor cell may be similiarly dependent, if it passively aquires suppressive abilities from soluble factors. A third non-indomethicin sensitive cell may develop as an expansion of the Ts pool.

V. MLR Stimulation of Human Peripheral Blood Lymphocytes

Studies of human peripheral blood lymphocytes for HLA typing by Sheehy et al [39] revealed the presence of an antigen specific T suppressor cell for HLA-D antigens. In vitro primed cells were able to inhibit a primary response on the part of unprimed cells, and the inhibition was specific and restricted to HLA-D compatibility. They determined that cytotoxicity (stimulated by HLA-A and -B differences) was not involved in this suppression. Other investigators [40] have demonstrated the same phenomenon using soluble Dr antigens to stimulate T suppressor cells which are Dr restricted. The suppression is mediated by a soluble factor displaying antigen specificity and D antigen restriction as well.

Goeken et al [41] have investigated some of the differences between ConA induced and MLR induced suppressor cells. The ConA induced suppressor cells are characteristically mitomycin sensitive and antigen non-specific. MLR induced suppressor cells exhibit antigen specific suppression unless very high numbers of suppressor cells are used. Cells repeatedly stimulated by alloantigens will express only alloantigen specific responses,

and are significantly mitomycin resistant.

Goeken suggests that mitogen induced suppressor cells may be suppressor inducer cells, and MLR induced suppressor cells may be the actual effector suppressor cells. Other investigators [42] suggest two separate mechanisms designed to modulate and fine tune antigen specific responses.

VI. Monoclonal Antibody Markers

T lymphocyte subclass identification by monoclonal antibody markers [43] initially divided human peripheral blood T cells into an OKT4(+) helper/inducer population and an OKT8(+) suppressor/cytotoxic population. Additional work has suggested functional heterogeneity within the OKT4(+) and OKT8(+) populations. Thomas [44] et al described a PWM activated OKT4(+) cell able to exert potent feedback suppression on B cell differentiation. The suppression effected by the OKT4(+) cell required the presence of a resting OKT4(+) subpopulation. Additional work [45] identified a new differentiation antigen OKT17 present on a subset of OKT4(+) activated cells that functionally identified the suppressive subpopulation. Furthermore, an OKT2O antigen identified the cytotoxic cell subgroup in an activated OKT8(+) population.

Both the OKT4(+) and the OKT8(+) cells described by Thomas et al are radiosensitive suppressor cells. Their work concurs with that of Mizerski describing radiosensitive suppressor cells of T cell mitogenesis.

Suciu-Foca [46] et al examined MLR stimulated suppressor T cells. Alloantigenic priming activated OKT4(+) and OKT8(+) cells capable of expressing Ia antigens and of inducing HLA-D restricted suppression.

It is interesting that Sakane and Green described two suppressor cells; one for T cell mitogenic responses, and one for responses to B cell mitogens (PWM) and alloantigens. Their work suggests that the OKT4(+) cell described by Suciu-Foca (alloantigen produced) and the OKT4(+) cell described by Thomas are contained in the same subset.

Initially, OKM1 was thought to be a specific MØ marker. More recent work [47] suggests that OKM1 is a marker shared by MØ, a subpopulation of T cells, and natural killer cells. Development of the monoclonal antibody OKM5 may allow elucidation of MØ suppressor activity.

MATERIALS AND METHODS

I. Cell Isolation

Sixty to eighty milliliters of peripheral venous blood was drawn from twelve normal human donors ranging in age from 25 to 35 years. Human mononuclear cells were separated on a Ficoll-Hypaque gradient, washed three times in Hanks basic salt solution (HBSS) (Irvine) supplemented with 3% fetal calf serum (FCS), 1% penicillin-streptomycin, and 1% garamycin.

II. Generation of ConA Suppressor Cells

Separated peripheral blood lymphocytes were cultured for three days in ten ml dishes at a concentration of 2.5-3 x 10^6 cells/ml in a media containing 3% rabbit serum (RS), 5% FCS, 3% minimal essential medium supplement (MEM SUP), 1% penicillin- streptomycin, 1% garamycin, 1% fungizone, .5% asparagine, 1% l-glutamine, and 5 x 10^{-3} 2-mercapto-ethanol. Concanavalin

A was used at a final concentration of 25 micrograms/ml to 100 micrograms/ml. Optimal mitogenic stimulation of ConA suppresssor cells varied both among individuals, and within the same individual on different occasions.

III. Generation of MLR Suppressor Cells

Initially, a routine MLR screening of donor lymphocytes as responders and stimulators was done. Donors for MLR generation of suppressor cells were selected from high responder:stimulator combinations when possible. Stimulator cells at a concentration of 1×10^7/ml were mitomycin C treated with 25 micrograms/ml at 37^o centigrade for thirty minutes, and washed three times in HBSS. The MLR induced suppressor cells were produced by coculturing 1×10^6/ml responder cells with 5×10^5/ml stimulator cells in ten ml of MLR media. Cells were washed three times before use.

IV. Assay System

MØ production of plasminogen activator (PA) was assayed. The MØ were isolated from the peripheral blood mononuclear cells by selective adherence to Douglas-Ackerman flasks, and incubated 24 hours to remove polymorphonuclear cells. Sixteen millimeter multiwell dishes coated with commercial human I-125 fibrinogen were activated by the addition of thrombin. The plates were incubated at 37^o centrigrade for one hour to allow fibrin formation. The wells were then washed two times with HBSS. The previously isolated PB monocytes were added in media containing either 10% acid treated FCS, 10% FCS in 100 micrograms/ml soybean trypsin inhibitor (to prevent plasmin mediated fibrinolysis), or 10% FCS and 200

micrograms/ml soybean trypsin inhibitor.

The cells were incubated at 4 x 10^5/well (0.4ml) for 24 hours. Supernatants were withdrawn and collected and the wells washed two times with HBSS. After washing, fresh media was added to the wells, and the supernatants withdrawn 24 hours after and counted in the Beckman Biogamma Counter. Raw data (counts) are corrected for soybean trypsin inhibitor and no cell lines, and expressed as percent plasma mediated fibrinolysis.

V. Addition of Suppressor Cells

The ConA generated or MLR generated suppressor cells were harvested, washed 3 times, and resuspended at either a concentration of 5 x 10^6/ml or an equivalent concentration to positively selected FACS cells. Cells were added to the isolated MØ described above.

VI. Monoclonal Antibody Treatment

The monoclonal antibodies OKT8, OKT4, and OKM1 (Ortho) were used to selectively lyse subpopulations of cultured cells. Mononuclear cells at a concentration of 5 x 10^7 (.25ml) were incubated with .25 ml of a 1:250 dilution of the antibody at room temperature for 45 minutes. The cells were then spun down, the supernatant aspirated, and .25ml of 1:10 dilution of low toxicity rabbit complement (Cappel) was added. The cells were resuspended and incubated at 37^o centrigrade for one hour, washed 3 times, and counted. Cells were added to the isolated MØ described above at a concentration of 5 x 10^6 cells.

VII. Fluorescence Activated Cell Sorting

Positive selection of suppressor cell subpopulations by means of the Fluorescence Activated Cell Sorter (FACS II) was done using fluoresceinated OKT8 and OKT4 (Ortho). Mononuclear cells at a concentration of 5 x 10^7 (.25 ml) were incubated with .25 ml of 1:100 dilution of fluoresceinated antibody for 45 minutes in the dark on ice. Cells were washed three times and diluted to a final concentration of 1 x 10^6/ml for sorting. Both MLR generated and ConA generated cells were sorted and assayed for their effect on MØ production of plasminogen activator. Additionally, the OKT8(-) cells were collected from the FACS sorter and assayed for their effect on MØ PA production.

RESULTS

I. Results of ConA Depletion Experiments

Elimination of OKT8(+) cells from ConA generated suppressor cells resulted in significant but incomplete abrogation of suppression (Table 1). Normal peripheral blood monocyte production of plasminogen activator was measured (control). Cells from the same donor assayed at the same time, but with either ConA generated suppressor cells, or ConA generated cells treated with OKT8 and complement showed a significant difference in PA production.

The addition of 5 x 10^6 ConA suppressor cells reduced MØ PA production from 39-54% of normal. Pretreatment of Con suppressor cells with OKT8 and low toxicity rabbit complement resulted in an average of 52% abrogation of suppression when added in equal numbers. This abrogation of

suppression was not due to complement protein interference. To check this, in some experiments (421, 422a) non lytic complement was used. This resulted in no significant abrogation of suppression.

TABLE 1. Suppression of MØ PA production by ConA activated cells and OKT8 depleted cells

exp. no.	donor	control (PA content as % fibrinolysis)	conA cells	percent suppr.	OKT8 depld	percent suppr.
321	SB	46.5	25.2	46%	35.1	25%
328	MM	33.3	24.7	26%	30.0	10%
387	BS	79.5	46.1	42%	60.1	25%
399a	RW	37.8	17.5	54%	23.7	27%
399b	RW	37.8	20.5	46%	32.9	13%
418	EH	49.8	30.2	39%	43.5	13%
423	CY	37.8	28.1	26%	42.2	-12%
430	TB	26.3	13.6	48%	17.5	33%
421	RW	38.5	28.6	26%	29.6	23%
422a	JM	49.7	37.9	24%	34.6	30%

ConA cells and OKT8 depleted cells were at a concentration of 5×10^6 cells.

In two experiments, the monoclonal antibody OKM1 was used to lyse a subpopulation of cells to assess their effect on suppression. OKM1 depletion also showed a partial abrogation of suppression (Table 2).

TABLE 2. Suppression of MØ PA production by ConA activated cells and OKM1 depleted cells

exp. no.	donor	control (PA content as % fibrinolysis)	conA cells	percent suppr.	OKM1 depl.	percent suppr.
387	BS	79.5	54.0	32%	68.5	14%
399a	RW	37.8	17.5	54%	30.7	19%
399b	RW	37.8	20.5	46%	27.0	29%

II. Results of FACS Sorting Experiments

ConA generated suppressor cells were labelled with fluoresceinated OKT8 antibody, and positively selected using the Becton-Dickinson FACS II cell sorter. This technique generally yields 95% pure cells. In addition, the FACS sorter was gated to abort weakly staining cells. The addition of 1 x 10^6 OKT8(+) suppressor cells showed significant suppression of MO PA production (Table 3). Addition of the negatively selected OKT8(-) cells also resulted in suppression of MØ PA production. This OKT8(-) population could have been contaminated with approximately 5% OKT8(+) cells, but the strong suppression seen with the OKT8(-) cells suggests the presence of additional suppressor cells. The FACS selected cells effected suppression at 20% of the concentration of unseparated cells. FACS sorted cells at a concentration of 1 x 10^6 cells suppressed to the same degree as unsorted ConA stimulated cells at a concentration of 5 x 10^6 cells. FACS sorting for OKT8(+) cells enriched for a suppressor population, and showed a 4 to 5 fold increase in activity over unseparated cells. (Cell

population analysis indicated 12-20% of lymphocytes separated were OKT8(+). At equal concentrations, unseparated cells were weakly suppressive (Table 3).

TABLE 3. Positively selected ConA stimulated cells result in significant suppression of MØ PA production

exp. no.	donor	control (PA content as % fibrinolysis)	conA cells	% supr.	T8(+)	% sup.	T8(-)	% sup.
422	JM	49.7	37.9	24%	37.9	24%	ND	
428	BS	43.3	36.6	16%	31.9	26%	ND	
430	TB	26.3	13.3	48%	21.7	17%	20.2	23%
432	EH	62.3	[d]58.4	6%	42.4	32%	49.6	20%
428	BS	43.3	[d]39.9	8%	31.9	26%	ND	

Positively selected ConA generated cells were added at a concentration of 1×10^6 to normal human PB MØ. The superscript (d) denotes ConA cells added at a concentration of 1×10^6, rather than 5×10^6.

III. Effect of PGE 2 on Suppressor Cell Generation

In some experiments (Table 4) PGE 2 at a concentration of 1×10^{-6}M was added to assess the effect on generation of ConA induced suppressor cells. The effect was variable, both between individuals, and with the same individuals on different days. No consistent effect could be attributed to the addition of PGE 2 in the generation of suppressor cells acting on a facilitory monocyte.

TABLE 4. PGE 2 had a variable effect on the generation of ConA suppressor cells when added at 1 x 10^{-6}M

exp. no.	donor	control (PA content as % fibrinolysis)	conA/PGE2	percent suppr.	conA only	percent suppr.
414[a]	BS	69.7	45.8	34%	40.1	42%
414[b]	BS	69.7	44.0	37%	53.9	33%
418[b]	EH	49.8	30.2	39%	40.5	19%
422	JM	49.7	38.5	23%	37.9	24%
428[a]	BS	43.3	37.7	13%	35.7	18%

[a] denotes conA concentration of 50 micrograms/ml

[b] denoted conA concentration of 100 micrograms/ ml

IV. Effect of MLR Suppressor Cells

Initial investigation of the effect of alloantigen generated suppressor cells indicates that a population is generated that can suppress MØ PA production. The suppression of MØ PA production is less that that seen with equivalent numbers of mitogen stimulated suppressor cells.

Table 5. Suppression of MØ PA production by MLR generated suppressor cells

experiment number	donor	control (PA content as % fibrinolysis)	MLR cells	percent suppr.
422	RW	28.7	25.2	12%
431	NC	35.4	25.7	27%
435	MT	45.7	41.7	8%
436	RW	63.4	52.2	18%

DISCUSSION

Suppression of facilitory MØ activity is correlated with depression of T cell mitogenic (PHA) responses and can have broad clinical consequences. Elucidation of suppressor cell subsets responsible for facilitory MØ activity may represent deletion of a subpopulation of MØ, a change in function of a multifunctional cell, or a shift in the ratios of MØ helper to suppressor populations. Ia expression on MØ may determine the target population, and is an area for further investigation.

The data reported above describes an OKT8(+) cell generated by ConA responsible for 50% or greater suppression of MØ PA production. Deletion of the OKT8(+) cells resulted in significant abrogation of suppression. An average of 40% of the ConA stimulated cells were lysed by OKT8 and complement in the deletion experiments. In the enhancement experiments (FACS), only 12-20% of the ConA generated cells stained as OKT8(+) cells. The cell numbers after lysis compared to the numbers positively stained was probably due to cell loss during multiple washing of the OKT8 depleted cells. The suppression of the PA still remaining after OKT8 depletion could be due to an OKT4(+) cell, or a MØ suppressor cell. Since cell numbers were kept constant, the remaining cells represent an increased concentration of OKT8(-) cells. Also, OKT8 cells with antigenic density too low for lysis may be in the population. Initial experiments to determine the presence of a MØ suppressor (OKM1) were begun, but discontinued due to the lack of specificity of the OKM1 antibody. Further investigation with a specific monoclonal antibody should address this question.

The enhancement (FACS) experiments support the presence of an OKT8(+) suppressor cell. Suppressive activity was enhanced 4 to 5 fold over unseparated Con A activated cells. The FACS sorted OKT8(-) cells also demonstrated suppression. Additional sorting for OKT17(+) or OKM5(+) cells may elucidate the phenotype of the suppressor cell in the OKT8(-) cells.

The addition of 1×10^{-6}M PGE 2 had no consistent effect on generation of suppressor cells. This may be due to differences in the relative proportions of suppressor subpopulations stimulated at different times. Marked differences in responses to Con A were noted in the same individuals on different dates, and may reflect subtle differences in immune status at those times. Also, enough PGE 2 may have been generated in the Con A cultures so that additional PGE 2 did not consistently improve generation of suppressor cells.

Initial attempts to generate MLR suppressor cells indicate that a subpopulation of suppressor cells do affect MØ facilitory activity. Goeken found that alloantigen generated suppressor cells showed a fifty fold decrease in suppressive ability compared to mitogen induced suppressors. It has been shown that MLR generated suppressor cells express increased Ia on their cell surface. Ideally, FACS isolation of specific subpopulation of MLR generated cells (OKT17+, OKT8+, and OKM5+) would provide the opportunity to quantitate suppressor cell numbers without the addition of large numbers of MØ. Double selection of Ia(+) suppressor cells should elucidate specific suppressor effectors.

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FOOTNOTES

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