IMMUNOREGULATION AND AUTOIMMUNITY

Proceedings of the Third Immunodynamics Conference, The Cleveland Clinic, Cleveland, Ohio, USA, May 12–13, 1980

Editors:

RANDALL S. KRAKAUER, M.D.

MARTHA K. CATHCART, Ph.D.

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Preface

We conceived the idea of a conference and publication on immunoregulation and autoimmunity at a time when it appeared we were rapidly approaching the key to the pathogenesis and potential immunotherapy of a wide variety of autoimmune diseases and felt that a conference of noted scientists in the field would result in an exchange of ideas to accelerate the pace of research and provide future direction. We also felt that the resulting publication would serve as both a compendium of the state of the art and a manual for investigators in the field. If in five or ten years half of this material proves to be substantially correct, we will consider this volume a success and if at least one major idea proves to be prophetic, we shall consider this success to have been phenomenal.

I also report a discordant note symptomatic of discordant times. Doctor Alexander Lerner of Moscow, RSFSR, was invited to participate in this symposium and regrets to inform us that the policies of his government do not leave him at liberty to accept such invitations. Other than our displeasure and grief over this wound to international science, we find no additional comment necessary.

I wish to thank those whose tireless assistance and efforts have made this conference and publication possible, including Doctor Martha Cathcart, my Co-editor; Joan Skiba, Conference Coordinator; David Ilfeld, Chairman of the Poster Sessions; the individual session chairmen; and for their valuable advice and assistance, Doctors John Clough and Max Proffitt. I indirectly wish to thank my children, Meryl, 4 and Ari, 2, who I hope someday will forgive the time their father spent on this conference instead of with them.

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I

Mechanisms of Autoimmunity

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AUTOLOGOUS MIXED LYMPHOCYTE REACTIVITY: A MODEL FOR IMMUNOLOGICALLY RELEVANT SELF RECOGNITION

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INTRODUCTION

Studies in rodents have clearly demonstrated that macrophages (MØ) constitute an absolute requirement for the controlled expression of T cell immunity[1,2]. For example, activation of antigen reactive helper T cells and effector T cells required for delayed hypersensitivity requires that they not only recognize nominal determinants in antigen but also MØ glycoproteins coded for by immune response associated (Ia) genes of the major histocompatibility complex[3,4]. In the absence of MØ, soluble antigen will not activate reactive T cells. However, several laboratories have indicated that in the absence of antigen, both human and murine T cells can be induced to proliferate during co-culture with autologous MØ[5-8]. The relationship between the T cells proliferating in this autologous or syngeneic mixed lymphocyte reaction (AMLR) to those T cells required for either reactivity to conventional antigen or helper cell activity has not been precisely determined. The following data suggests that human T cells activated in the AMLR by autologous MØ are required for reactivity to soluble antigen and can provide helper influences necessary for maximal immunoglobulin (Ig) synthesis.

MATERIALS AND METHODS

The AMLR was performed as previously described[5]. Responder populations consisted of E-rosette positive populations (> 90% T) while stimulator cells were derived from mitomycin treated, adherent peripheral blood mononuclear cells (> 90% phagocytic, > 95% esterase positive). Utilizing a MØ specific, monoclonal antibody, we have previously shown that the stimulator cell existing among this population is indeed a MØ (H. Raff and J. Stobo, J. Exp. Med. In Press). The AMLR was performed utilizing two ratios of responder to stimulator cells (2/1, 1/1) cultured for two periods (6 days and 9 days) in 10% heat inactivated autologous serum. Results are presented either as maximal CPM in cultures

containing responder and stimulator cells or as the maximal stimulation index (S.I.). Proliferative reactivity to soluble antigens and pokeweed mitogen (PWM) induced Ig synthesis was performed as previously described[5,9].

Negative selection of proliferating T cells with 5-bromo-2-deoxyuridine (BUDR) was performed as outlined previously[5]. Cytolysis with T-29, a monoclonal T cell specific antibody was accomplished with a sandwich cytotoxicity technique (T cells + T-29 + goat anti-mouse Ig + C).

RESULTS AND DISCUSSION

To determine the relationship between T cells reactive in the AMLR to autologous MØ and those responsive to conventional antigens, two techniques were utilized. First, negative selection with BUDR and light was used to selectively remove those T cell proliferating in response to autologous MØ. T cells were incubated with MØ and BUDR. One-half of the cultures were not exposed to white light while the other half were. The subsequent proliferative reactivity of the two populations to either autologous macrophages or to the soluble antigens *Candida albicans* and purified protein derivative (PPD) were then compared (Table 1).

TABLE 1

REACTIVITY OF MØ RESPONSIVE AUTOLOGOUS T CELLS TO SOLUBLE ANTIGENS

Negatively Selected Populations		Maximal Reactivity		
		Aut MØ[1]	Candida[2]	PPD[2]
Exp #1	T + MØ + BUDR, No Light	4350	5451	1713
	T + MØ + BUDR, Light	1840	210	139
Exp #2	T + MØ + BUDR, No Light	1719	13172	32855
	T + MØ + BUDR, Light	619	4763	6628

[1]Maximal Reactivity expressed as CPM.

[2]Maximal Reactivity expressed as ΔCPM.

Note that T cells remaining after this negative selection demonstrated a marked decrease in their subsequent response to autologous macrophages. Most importantly, these same cells also demonstrated a marked decrease in their reactivity to the two soluble antigens. Three points concerning this data

should be emphasized. First, although the subsequent reactivity to autologous macrophages is represented as CPM, it can be demonstrated that the S.I. to autologous macrophages among cultures receiving both BUDR and light was less than 1.3. Second, similar negative selection experiments utilizing autologous B cells, which we have previously shown to represent a distinct stimulator population in the AMLR, failed to diminish, and in one case augmented, the subsequent T proliferative reactivity to antigens. Third, BUDR and light negative selection of T cells proliferating in response to autologous macrophages did not diminish their subsequent proliferation in an allogeneic mixed lymphocyte reaction. These latter two findings argue against a non-specific decrease in reactivity induced by BUDR and light treatment. (The finding that negative selection of the MØ responsive T cell did not diminish subsequent alloreactivity does not indicate that this population of autologous reactive T cells is not alloreactive.)

To further define the relationship between antigen reactive T cells and those responsive to autologous macrophages, we produced a monoclonal antibody with specificity for macrophage responsive T cells. BALB/c mice were immunized with T cell blasts generated during an AMLR. The spleen cells were then fused with the murine plasmacytoma, NS-1, and clones producing antibody against T cells reactive to autologous MØ selected[10]. One of the clones produced an antibody termed T-29 which reacts in immunofluorescence and cytotoxicity assays with 9.8 $\pm$ 2.3% of the peripheral blood T cells but not with B cells or MØ from several HLA-DR disparate individuals. This antibody was then tested for its ability, in a sandwich cytotoxicity assay, to remove T cells responsive to autologous MØ and soluble antigen. In these experiments, reactivity to antigen was measured either by proliferation or by the production of the lymphokine, leukocyte inhibition factor, with the results expressed as % inhibition of leukocyte migration. Note (Table 2) that when compared to T cells treated with the control reagent, mouse immunoglobulin (MIg), T cells remaining after cytolytic treatment with the monoclonal antibody T-29 demonstrated a substantial diminution in their subsequent ability to respond to autologous MØ. Most importantly, this same population was deficient in antigen reactivity as measured either by proliferation or by lymphokine release. Thus, negative selection experiments utilizing either BUDR and light or cytolysis with the monoclonal antibody, T-29, indicate that T cells responsive in the AMLR to autologous MØ are also required for reactivity to conventional antigens.

TABLE 2

REACTIVITY OF T-29$^+$ CELLS TO AUTOLOGOUS MØ AND ANTIGEN

Treatment of Responding Populations		Maximal Reactivity		
		Aut. MØ	Candida	
		CPM	ΔCPM	% Inhibition of Migration
Exp #1	T + MIg + C	12311	13499	22%
	T + T-29 + C	925	2684	0
Exp #2	T + MIg + C	2895	5924	21%
	T + T-29 + C	887	48	4%

The next experiments indicate that the MØ responsive autologous T cells depicted by the monoclonal antibody T-29 are also required for maximal synthesis of immunoglobulin induced by the polyclonal mitogen, pokeweed. T cells were cytolytically treated either with the control reagent, MIg, or with T-29. The populations were then resuspended to a comparable frequency of viable cells and added in a ratio of 3:1 to autologous populations depleted of T cells but enriched for B cells and MØ. The cell mixtures were then incubated for 7 days with two concentrations of PWM and the amount of Ig synthesized and released into the culture media determined by competitive binding radioimmunoassay. Results are expressed as μg of Ig synthesized per 10^6 cells (Table 3).

TABLE 3

REQUIREMENT FOR MØ RESPONSIVE, T-29$^+$ T CELLS IN MAXIMAL, PWM INDUCED SYNTHESIS OF Ig

Treatment of Added T		μg Ig Synthesized/10^6 Cells
Exp #1	No T Added*	1.3
	T + MIg + C	35
	T + T-29 + C	15
Exp #2	No T Added*	0.2
	T + MIg + C	5
	T + T-29 + C	0.3

*Represents Ig synthesized by B + MØ cell population alone.

When compared to the amount of Ig synthesized by the T depleted, B and monocyte population alone, mixtures containing control T cells demonstrated a