The Pathophysiology of Human Immunologic Disorders

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Preface

I personally find most introductions extremely dull. Yet there they are, invariably thrust into the forefront of every textbook. They are intended to encourage you to buy the book. That seems contradictory, since something that turns you off is not likely to encourage you to read on. In your typical introduction, a few paragraphs are devoted to each chapter; they first briefly summarize the content and then tell you why you should read it. The effect is like a collection of good shirts just back in a semilyophylized state from a bad laundry. The concluding section tells of the nice things people did to help get the book out. Rather than introducing the book in such a pedantic fashion, let me tell you why I undertook this one.

In immunology, research with experimental animals has held center stage for many years. The sophistication of experimental immunology lured many young investigators and garnered prominence at scientific meetings and in the literature. This trend was also cause for concern. Would intellectual gratification take precedence over clinical urgency? Would this burgeoning mass of experimental data ever prove applicable to human systems? Would taxpayers tire of funding research that seemed preoccupied with mice, guinea pigs and chickens, rather than mankind?

While experimental immunobiology was experiencing rapid growth, clinical immunology was in a decline. Students found even the most obscure of immunologic syndromes detailed in many texts but had to turn to animal models to learn how the immune system worked. The absence of inbred human models and the red tape needed to keep human experimentation within ethical boundaries discouraged students from careers in clinical investigation. Perhaps we fell short at the bedside by not generating enough enthusiasm about important questions raised by disease.

Clinical investigation has recently picked up considerable momentum. This surge is largely due to technical developments such as the hybridoma technique for producing monoclonal antibodies and cell sorting. This new information can be readily applied to clinical settings. The similarities that are emerging between human and animal systems have clearly vindicated the basic scientist. Experience with basic immunology is suggesting new approaches to clinical problems. The leap from cage to bedside has been taken.

This recent union of basic and clinical immunology is permitting incisive research on clinical problems. Old concepts are being remolded. Ideas for new research are appearing at a remarkable rate and undoubtedly exceed the funding available to undertake many projects that would benefit humanity. It is time to pause and take stock. In effect, this book examines where we stand regarding human immunobiology and immunopathology in 1981. It is compiled in editorial style, in the hope that it will evoke ideas for further investigation while you read. That is why I undertook this book.

For those of you who do not know, compiling a textbook is a lot of work. It will not make you rich. It will not justify additional funds for your own research. Your peers will not think any more of you as an investigator after reading it. The fact is that it is a work of personal gratification. My gratification will be enhanced if you enjoy reading our book.

Nobody has the time to author a complete textbook anymore. Indeed, our interests have become so focused that there are few scientists with the range of information that would justify complete authorship. Nowadays you edit a book and call upon colleagues to "contribute" chapters. This is where the trouble begins. Initial enthusiasm is replaced by exasperation with the

encroachment this makes upon the contributor's time, already overcommitted. Those that are punctual remind you that their chapters are not like Bordeaux and do not improve with age while awaiting others that are tardy. Most chapters are delivered to the editor with pride. You must be careful not to hurt this pride when making suggestions as to how the manuscript could be improved or made to conform with the overall style of the text.

The caliber of scientists who joined in this venture is gratifying. The literary style of conventional reviews was vetoed because compulsive overcrowding of data destroys literary composition. Yet another description of clinical syndromes was redundant. Basic experimental immunobiology could only serve as background for human systems which receive unashamed priority herein. Bibliographies were to identify sources of information and not to serve as a substitute for a literature search when preparing future manuscripts. Instead, contributors to this book were asked to present their views on specific topics. That should not be cause for concern. Divergent opinion has often served as a catalyst for important research. This interest in the future is the spirit of this book.

A few comments are indicated about the spirit to whom this book is dedicated. Daniel Twomey grew up in rural Ireland during the convulsions that preceded the birth of the Republic. He practiced medicine in this countryside for 30 years. There is no record of the many textbooks and medical journals he read by candlelight during those years. He would not take vacations in case "somebody might get sick" while he was away. He was humble enough to attend the funerals of deceased patients, but too proud to attend if the family had called in another general practitioner on the case! He serves as a constant reminder to me that the raison d'etre for medical research is to improve the lot of my fellow man.

JEREMIAH JOHN TWOMEY

Contents

Chapter 1

Human T Cell Differentiation

Leonard Chess and Yolene Thomas

Introduction

The induction and physiologic regulation of B cell differentiation is governed in large part by T cells and, perhaps more importantly, by interactions among T cells (Armerding and Katz, 1974; Cantor et al., 1976, Cantor and Boyse, 1977a). One of the major paradigms to emerge during the last decade is that the various homeostatic immunoregulatory functions of T cells are effected by distinct subsets of T cells that can be distinguished by cell surface differentiation antigens. Antibodies to these surface differentiation antigens are extremely useful tools in identifying and isolating these subsets. For example, the evidence for functional subsets of murine T cells came from the elegant studies by Cantor and Boyse (1977a and b) which demonstrated that genetically defined cell-surface alloantigens (lyt) can be used to identify and isolate functionally distinct T cells at different stages of differentiation.

Recently, using the technique of Köhler and Milstein (1975) for the production of myeloma-lymphocyte hybrid cell lines, monoclonal antibodies reactive with human T cell surface antigens have produced. To date, the most extensive series of monoclonal antibodies which have been developed are the OKT and Leu series (Engleman et al., 1981; Evans et al., 1981; Kung et al., 1979; Ledbetter et al., 1981). For ease in discussion and data evaluation, we will largely restrict our discussion of these reagents to the OKT series of monoclonal antibodies since these have been the best characterized to date from a functional point of view. These antibodies were functionally assessed in earlier studies by Reinherz et al., (1979a and b, 1980a and b), and more recently by our laboratory and others (Biddison et al., 1981; Friedman et al., 1981; Janossy et al., 1980; Thomas et al., 1980, 1981a, b and d). The OKT3 antibody defines an antigen present on most human peripheral T cells (90 to 95%), the OKT4 antibody identifies 50 to 60% of human T cells and the OKT8 antibody identifies 30 to 40% of human peripheral T cells. Interestingly, initial studies demonstrated that the T cell marker, OKT4, is directed at T cell sets containing helper cells, while OKT8 reacts with the suppressor and cytotoxic T cell effectors. More detailed analysis of these subsets, however, has demonstrated that this preliminary subdivision represents an oversimplification of the spectrum of T cell functional diversity.

In this review, we will concentrate upon some recent developments in our understanding of the functional properties of isolated T cell subsets, with emphasis on human T cell subset interactions in the induction and homeostatic control of B cell differentiation and T cell effector function. For example, it has been shown that the generation of suppressor-effector activity in human peripheral T cells requires cooperation between two subsets of cells: one within the

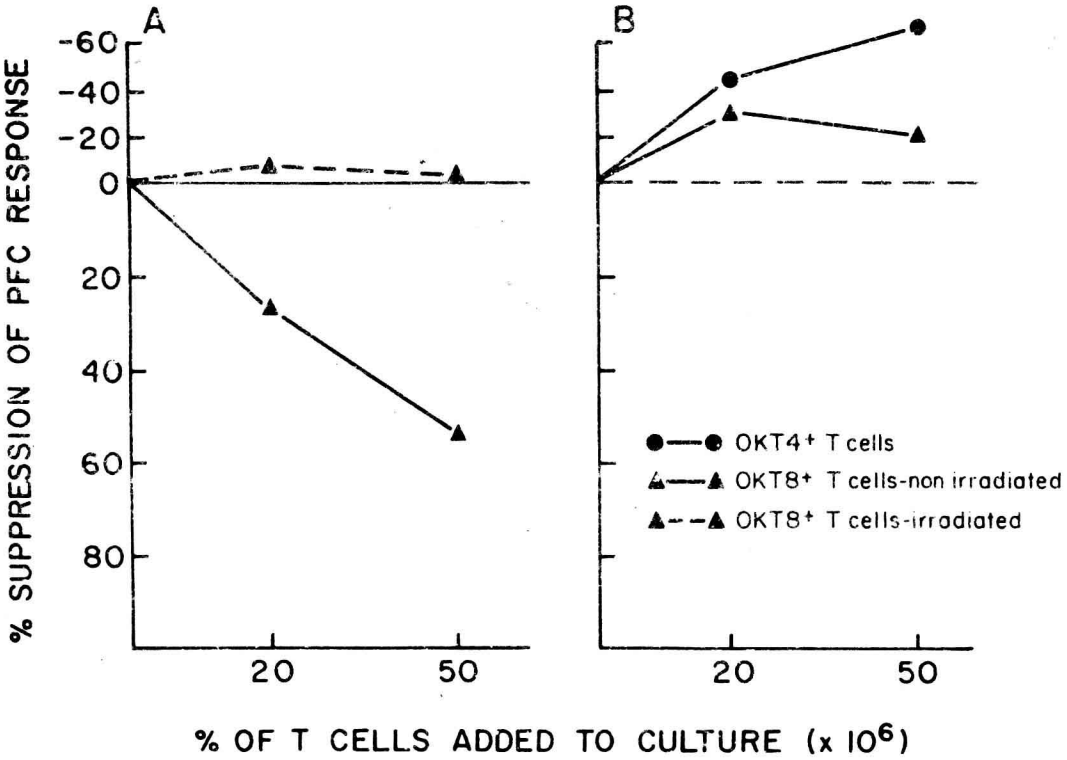

Fig. 1.1 Cooperative interaction between OKT4$^+$ and OKT8$^+$ is involved in the generation of suppressor activity. A) The standard cultures contained 0.1×10^6 OKT4$^+$ T cells and 2.0×10^6 B cells in addition to 10 μg PWM. To this system was added graded numbers of either untreated OKT8$^+$ T cells (▲——▲) or irradiated OKT8$^+$ cells (▲---▲). B) The standard cultures contained 1×10^6 irradiated OKT4$^+$ T cells and 2.0×10^6 B cells in addition to 10 μg PWM. To this system were added graded numbers of either OKT4$^+$ T cells (●——●) or OKT8$^+$ T cells (▲——▲). After 5 days, cultures were harvested and assayed for PFC activity. Suppression was calculated as follows:

$$\% \text{ Suppression} = 1 - \frac{\text{PFC (experimental culture)}}{\text{PFC (standard culture)}} \times 100$$

OKT4$^+$ population and the other within the OKT8$^+$ population. Moreover, evidence is emerging that there exists important functional heterogeneity within the OKT4$^+$ and OKT8$^+$ populations. The evidence for this heterogeneity arises from studies which have depended in part on the relative radiosensitivity of distinct immunoregulatory functions of cells contained within these sets and the use of additional monoclonal probes reactive with fractions of OKT4$^+$ and/or OKT8$^+$ cells. For instance, recent studies have revealed that the OKT4$^+$ T cell subset contains at least four distinct types of cells: radiosensitive helper cells; radioresistant helper cells; radiosensitive inducer of suppressor cells; and, after activation, radiosensitive suppressor cells. Furthermore, the radioresistant OKT4$^+$ helper cells and radiosensitive OKT4$^+$ helper cells can be identified and isolated by virtue of an additional cell surface antigen, OKT17. Since the Leu 3 monoclonal antibody identifies essentially the same subset as the OKT4 antibody, it is obvious that heterogeneity will also exist within the Leu 3$^+$ population. In other studies, functional microheterogeneity has been found within the OKT8$^+$ population (essentially identical in the Leu 2 population) and it has been possible to distinguish suppressor from cytotoxic cells after activation using newer monoclonal probes.

Functional Properties of Isolated Human Lymphocyte Subsets and Their Interactions

OKT8$^+$ Cells Require the Cooperation of Radiosensitive OKT4$^+$ Cells to Mediate Suppressor Activity

There is compelling evidence that distinct T cell subsets are involved in the regulation of B cell differentiation (Cantor et al., 1976; Gershon, 1974; Jandinski et al., 1976). However, with respect to the development of human suppressor and effector cells, the question arose whether or not obligatory interactions between different T cell subsets were required before suppressor activity could be expressed. One of the first indications that T-T interactions are essential for the development of mature suppressor T cells was reported in 1978 by Broder et al. They observed that in patients with T cell leukemias whose blast cells induced suppression of B cell differentiation the leukemic cells required radiosensitive normal T cells to induce suppression.

To formally address the possibility in normal individuals, we investigated whether OKT4$^+$ cells collaborated with OKT8$^+$ cells in mediating suppression in pokeweed mitogen (PWM) induced B cell differentiation. Thus, graded numbers of OKT8$^+$ cells were added to cultures containing purified B cells and either nonirradiated OKT4$^+$ (Figure 1.1a) or irradiated OKT4$^+$ cells (Figure 1.1b). As can be seen in Figure 1.1a, only the addition of nonirradiated OKT8$^+$ cells resulted in suppression of plaque-forming cell activity. In contrast (Figure 1.1b), when nonirradiated OKT8$^+$ cells were added to a mixture of B cells plus irradiated OKT4$^+$ cells, the suppression of immunoglobulin production did not occur. However, a complete suppressor effect was restored when small numbers of nonirradiated OKT4$^+$ cells were reintroduced into the cultures (Thomas et al., 1980). It is clear, therefore, that the absence of suppression observed in the presence of irradiated OKT4$^+$ cells is not due to unfavorable OKT4$^+$/OKT8$^+$ cell ratios. Taken together, these results demonstrate that cooperative interactions between two distinct populations of radiosensitive cells, one within the OKT4$^+$ population and the other within the OKT8$^+$ group, must occur before suppressor activity can be expressed. These data suggest also that OKT8$^+$ do not deliver negative signals to B cells alone, independent of OKT4$^+$ cells. Further evidence that OKT8$^+$ cells require OKT4$^+$ cells to suppress has come from experiments in which B cells triggered by helper factors in the absence of OKT4$^+$ cells could not be suppressed by OKT8$^+$ cells (Thomas et al., 1981d).

T Cell Subsets Involved in the Regulation of the Production (and/or Release) of MLC-Derived Helper Factor(s)

The mechanisms by which T cell subsets exert their regulatory influences on other T cell sets and B cells is only partially understood. Among these regulatory mechanisms, the release of soluble mediators which are known to play a role in T-T and T-B cooperation is of particular interest (Armerding and Katz, 1974; Geha et al., 1974; Marrack and Kappler, 1975; Pickel et al., 1976; Schimpl and Wecker, 1977). Therefore, experiments were undertaken to characterize the T cell subsets responsible for the production of helper function in response to alloantigens. Cell-free supernatants were obtained after 48 hours of culture of either unselected T cells, OKT4$^+$ or OKT8$^+$ cells cocultured with irradiated (2000 R) allogeneic stimulator cells. Varying dilutions of these supernatants were added to purified B cells and the induction of antibody synthesis was measured after 6 days of cell culture. The results depicted in Figure 1.2 clearly show that OKT4$^+$ responder cells, but not OKT8$^+$ cells, appear to be the predominant T cell subset involved in the production of allogeneic helper factor(s) that can trigger B cell differentiation.

Since, in several experiments, purified OKT4$^+$ cells produced a more potent supernatant than did unselected T cells, further experiments were conducted to explore a possible negative

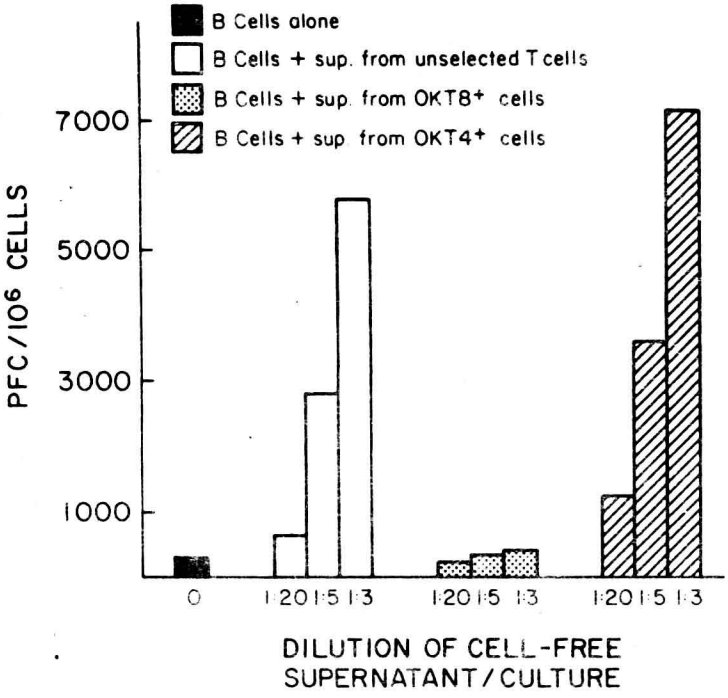

Fig. 1.2 OKT4$^+$ T cells produce MLC helper factor(s) which trigger B cell differentiation. Peripheral T cells were treated with anti-OKT8 + C. Residual viable cells (2×10^6) were then cultured with 4×10^6 T cell depleted, irradiated E negative cells. In control culture, unselected T cells were treated with complement alone. After 48 hours, various concentrations of cell-free supernatants were harvested and assayed for B cell helper activity after 6 days of culture. As control for B cell purity, additional B cell cultures were supplemented with PWM.

regulatory influence of OKT8$^+$ cells in the production of helper factors. Thus, increasing numbers of OKT4$^+$ cells, OKT8$^+$ cells or irradiated OKT8$^+$ cells were added to a constant number of OKT4$^+$ cells prior to activation; subsequently, the 48-hour cell-free supernatants were assayed for B cell helper activity. As shown in Figure 1.3, addition of graded numbers of unirradiated OKT8$^+$ cells progressively decreased helper factor activity. Conversely, further addition of OKT4$^+$ cells or irradiated OKT8$^+$ cells did not decrease this activity. Thus, the modulation by OKT8$^+$ cells in the production of helper factors is not simply the result of cell crowding but, rather, is due to an active suppression of OKT4$^+$ cells by radiosensitive OKT8$^+$ cells.

Functional Heterogeneity Within the OKT4$^+$ Population

The first evidence of functional heterogeneity of the OKT4$^+$ population was shown in studies of the regulation of B cell immunoglobulin production by the OKT4$^+$ subset (Thomas et al., 1980). For example, addition of graded numbers of radiosensitive OKT4$^+$ cells to B cells did not result in a linear increase of plaque-forming cells (which would be predicted if the OKT4$^+$ were exclusively inducer cells). Instead, decrease of the net helper activity was observed. Because of this observation, it was proposed that suppressor cells may be generated from precursors within the OKT4$^+$ population alone.

To address this possibility, we investigated whether OKT4$^+$ cells were able to suppress B cell differentiation independent of OKT8$^+$ cells after in vitro pokeweed mitogen activation. Thus, graded numbers of activated OKT4$^+$ cells were added to secondary cultures containing B cells and either nonirradiated fresh OKT4$^+$ cells (Table 1.1, part A) or irradiated fresh OKT4$^+$ cells (Table 1.1, part B). As shown in Table 1.1, part A, addition of activated OKT4$^+$ cells to cultures containing nonirradiated fresh OKT4$^+$ cells resulted in a reduction of the plaque-forming cell response. By contrast, addition of identical populations of activated OKT4$^+$ cells to cultures containing irradiated fresh OKT4$^+$ cells failed to decrease the plaque-forming cell response (Table 1.1, part B). However, addition of a small percentage of nonirradiated fresh

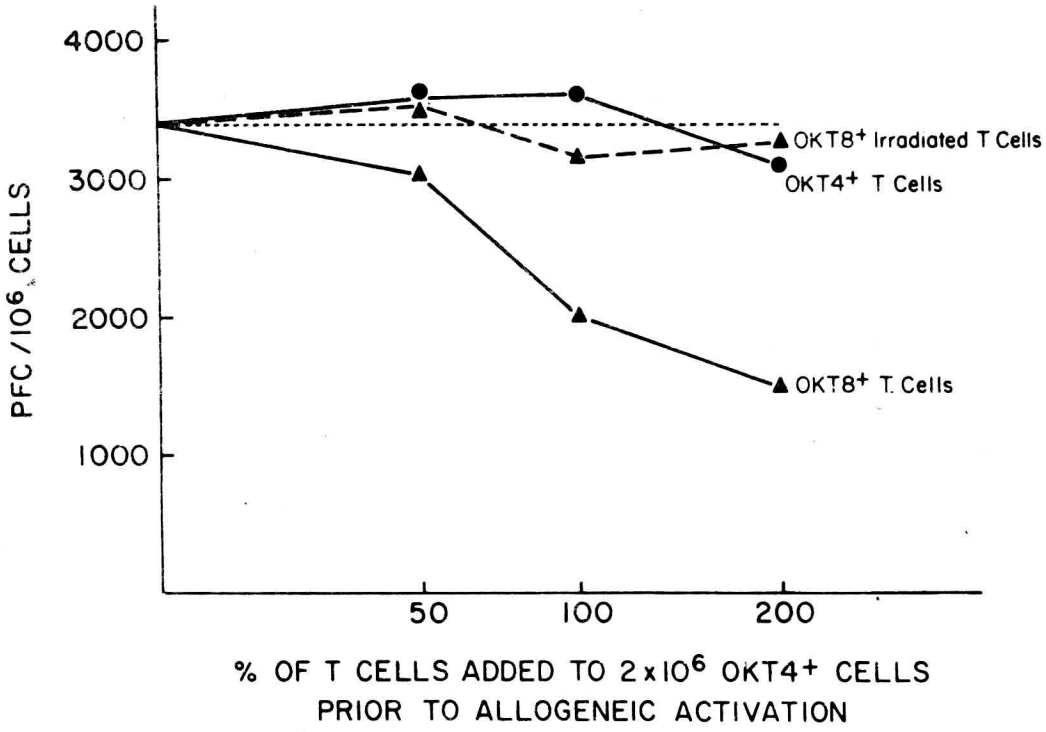

Fig. 1.3 Radiosensitive OKT8$^+$ cells regulate the production of MLC-derived helper factor(s); 2 × 10^6 OKT4$^+$ cells were cultured in the presence of graded numbers of either OKT4$^+$ cells (●——●), OKT8$^+$ cells (▲——▲) or irradiated (1250 R) OTK8$^+$ cells (▲---▲) prior to allogeneic activation. After 48 hours of culture, cell-free supernatants were harvested and then added at a final concentration of 33% to cultures of highly purified B cells. Each culture was assayed for PFC activity after 6 days of culture.

OKT4$^+$ cells (0.1 × 10^6) allowed for re-expression of suppression (Table 1.1, part C). These data strongly support the idea that suppression can be generated by polyclonal activation of the OKT4$^+$ subset. It should be noted that suppression induced by activated OKT4$^+$ cells is not secondary to the emergence of OKT8$^+$ cells in culture because: each population after activation maintained the original OKT3$^+$, OKT4$^+$, OKT8$^-$ surface phenotype when reanalyzed by immunoflourescence on the Cytofluorograf; and when activated OKT4$^+$ cells were treated with OKT4 or OKT8 in the presence of C′, only OKT8-treated (but not OKT4-treated) cells maintained their capacity to suppress B cells plus fresh OKT4$^+$ cells. We emphasize, however, that although activated OKT4$^+$ can exert potent feedback suppression, they can also function as helper cells in inducing B cell differentiation.

Further Dissection of the Functional Heterogeneity Within the OKT4$^+$ and OKT8$^+$ Populations by Additional Monoclonal Antibodies

Additional insight into the heterogeneity of OKT4$^+$ T cell function has been developed from studies using an additional monoclonal antibody, OKT17, reactive with a fraction of activated OKT4$^+$ cells (Thomas et al., 1981b). This antibody recognizes a cell surface antigen present on the majority of thymocytes and resting normal peripheral T cells. In contrast, OKT17 is unreactive with normal B cells, B cell lines, T cell lines or SIg$^+$CLL. Moreover, this monoclonal antibody is unreactive with null cells or macrophages. These observations demonstrate that OKT17 identifies a cell surface differentiation antigen unique to T cells. Interestingly,

Table 1.1 Suppression Mediated by Activated OKT4$^+$ Cells Requires the Presence of Radiosensitive Cells Within the Resting OKT4$^+$ Population

Numbers of Fresh OKT4$^+$ Cells Present in the Secondary Culture	Activated OKT4$^+$ Cells (First Culture) Added	PFC/10^6 Cells	Suppression (%)[b]
A. 0.1×10^6 non-irradiated	0	13,890 ± 1800	0
	0.2×10^6	8,100 ± 420	42
	0.4×10^6	7,500 ± 750	47
	1.0×10^6	5,190 ± 900	63
B. 1×10^6 irradiated	0	8,640 ± 608	0
	0.2×10^6	12,450 ± 2404	0
	0.4×10^6	12,600 ± 180	0
	1.0×10^6	8,310 ± 180	4
C. 1×10^6 irradiated + 0.1×10^6 non-irradiated	0	19,880 ± 300	0
	0.2×10^6	15,240 ± 1780	24
	0.4×10^6	9,440 ± 1321	53
	1.0×10^6	6,960 ± 600	65

[a] For 5 days, 2.0×10^5 fresh B cells were cultured in the presence of 10 μ_g of PWM. To these cultures various numbers of fresh OKT4$^+$ and activated OKT4$^+$ cells (first culture) were added.

[b] Suppression percentage was calculated as before (Fig. 1.1).

following activation, the antigen recognized by OKT17 is lost from a subset of OKT4$^+$ cells, but not from activated OKT8$^+$ cells. Thus, we investigated whether the OKT17 could serve as a marker to further dissect the functional heterogeneity within the OKT4$^+$ population. Graded numbers of activated unselected OKT4$^+$ cells as well as activated OKT4$^+$17$^+$ cells or OKT4$^+$17$^-$ were added to secondary autologous cultures containing B cells plus fresh OKT4$^+$ cells in the presence of PWM (Figure 1.4). Consistent with previous studies, activated unselected OKT4$^+$ cells suppressed B cell differentiation. The addition of small numbers of activated OKT4$^+$17$^-$ cells also suppressed B cell immunoglobulin production. In marked contrast, OKT4$^+$17$^-$ cells had minimal inhibitory activity. Thus, these data suggest that the suppressor cells within the activated OKT4$^+$ cells are restricted to a distinct subset of OKT4$^+$ cells bearing the OKT17 marker.

Although activated OKT4$^+$ cells can exert potent feedback suppression, activated OKT4$^+$ cells also contain helper cells. In particular, the helper function induced by activated OKT4$^+$ cells is relatively radioresistant. In contrast, the helper function mediated by fresh OKT4$^+$ cells is exquisitely radiosensitive over a wide range of T cell concentrations. Irradiated, unactivated OKT4$^+$ cells only induce B cell differentiation at high ratios of T cells to B cells. Because of these observations, we proposed the possibility that radiosensitive and radioresistant helper activities represent functions of distinct T cell subsets within the OKT4$^+$ population. Recent studies provide support for the presence of both a relatively radiosensitive, as well as a radioresistant, helper OKT4$^+$ population; these differ in terms of their reactivity with OKT17 antibody. For example, activated OKT4$^+$17$^-$ helper cells are radiosensitive, whereas activated OKT4$^+$17$^+$ helper cells are radioresistant (Figure 1.5 and Thomas et al., 1981b).

As mentioned previously, the reciprocal T cell population, OKT8$^+$, does not provide helper activity but contains cytotoxic effector cells and radiosensitive cells important in the suppression of B cell differentiation. Recently, Irigoyen et al., (1981) described a monoclonal antibody, PVR 11, which reacts with CTL effector cells within the OKT8$^+$ population but is unreactive with suppressor-effector cells. This dissociation of effector-suppressor and cytotoxic effect has been confirmed by other studies (Thomas et al., 1981c) using another monoclonal antibody, OKT20. This surface antigen is present on a small percentage of resting lymphocytes but is expressed in varying proportions on activated T cells. Functional analysis of normal resting human T lymphocytes demonstrated that the OKT20-depleted T cell subset was able to generate cytotoxic cells and to suppress antibody production to the same extent that OKT8$^+$ cells did. On the other hand, when unselected T

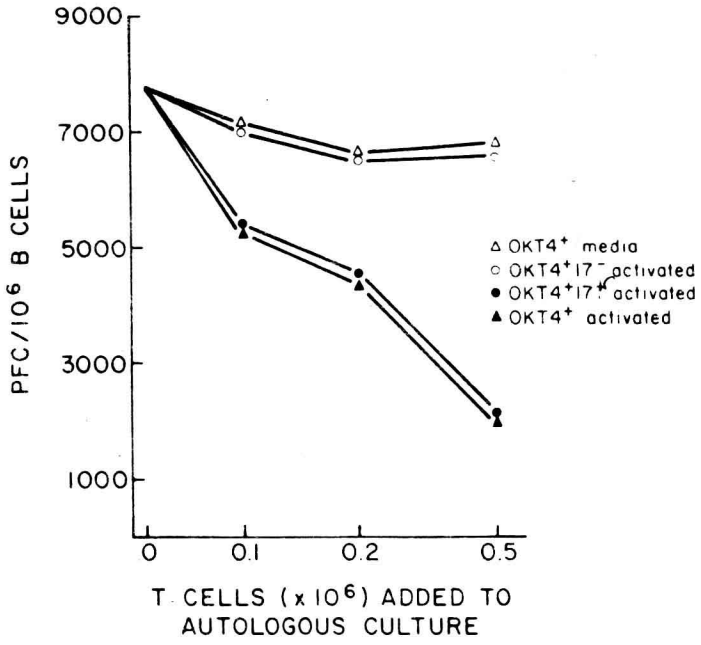

Fig. 1.4 Activated OKT4⁺17⁺ cells, but not activated OKT4⁺17⁻ cells, will suppress B cell differentiation induced by fresh OKT4⁺ cells. The standard culture contained 0.05×10^6 fresh OKT4⁺ cells and 1×10^6 B cells in addition to 10 μg of PWM. To this system were added graded numbers of either OKT4⁺ cells cultured with medium alone (Δ——Δ), OKT4⁺ cells, (▲——▲), OKT4⁺17⁻ cells (○——○) or OKT4⁺17⁺ cells (●——●) cultured with PWM during 60 to 70 hours of previous culture. After 5 days, cultures were harvested and assayed for PFC activity.

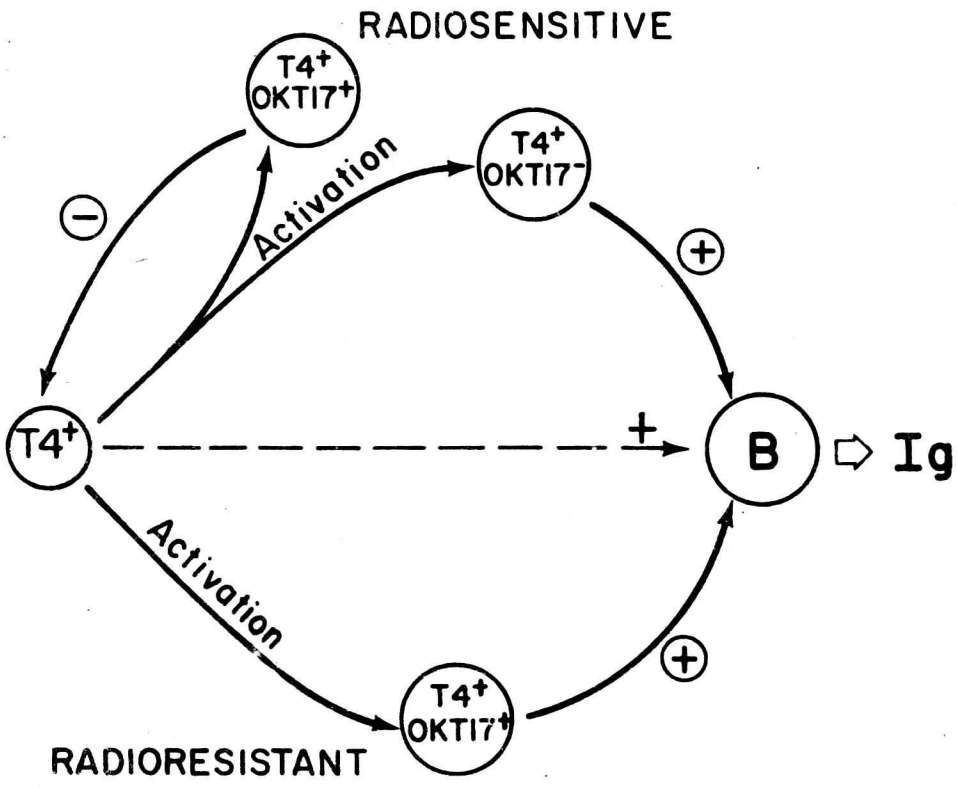

Fig. 1.5 Heterogeneity within the OKT4⁺ population.

lymphocytes were cultured for 6 days in mixed lymphocyte reaction and then depleted of OKT20 reactive cells, the cytotoxic effector T cells were eliminated. In contrast, OKT20-depleted T cells after identical activation were still able to suppress antibody production. Taken together, these data suggest that, following activation of $OKT8^+$ cells, the OKT20 differentiation antigen becomes selectively expressed on cytotoxic effectors but not on suppressor cells.

Summary

In this review we have focused on studies of the interactions of T cell subsets important in regulating human immune responses in normal individuals. These studies took advantage of the fact that, during the ontogeny of human T cells, functionally discrete subsets emerge that can be identified and isolated by virtue of distinct cell membrane differentiation antigens. These antigens, in turn, have been identified by monoclonal antibodies specifically reacting with the particular membrane differentiation antigens. Although we have presented evidence predominantly using the OKT series of antibodies, it is clear that other monoclonal antibodies identifying essentially identical populations will reveal similar functional properties. More importantly, the present data suggest that the currently available monoclonal antibody probes do not address the full range of functional subsets that exist within the human T cell peripheral pool.

In this regard, the evidence that the cell population identified by the OKT4 antibody contains at least four separable functional subsets including both helper and suppressor cells is of paramount importance. Whether these subsets contained within the OKT4 population arise from a common precursor or whether functionally distinct $OKT4^+T8^-$ cells emerge during thymic dependent differentiation is currently unknown. Additional monoclonal probes directed exclusively at fractions of $OKT4^+$ cells may allow for resolution of this problem. Until this question is resolved, the precise evolutionary relationship between human T cell subsets and murine T cell subsets will remain unclear. It is possible, for example, that contained within the $OKT4^+$ cells there exists a major precursor population analogous to the murine Lyt 1^+, 2^+, 3^+ subset which can be driven to differentiate along either helper or suppressor pathways. If such a cell exists, the current probes (OKT, Leu series, etc.) do not distinguish this population from the majority of differentiated helper cells. Thus, both helper cells and putative precursors are $OKT3^+$, $OKT4^+$, $OKT8^-$, Leu 3^+ and Leu

Despite the need for resolution of these ambiguities, the currently available monoclonal probes have been extremely useful with respect to the analysis of T-T and T-B interactions in man. The essential points to emerge so far are that suppressor cells contained within the $OKT8^+$ population require the presence of radiosensitive $OKT4^+$ cells in order for suppressor-effector function to be effected and the suppressor effects operate predominantly on $OKT4^+$ helper cells and not on B cells. In addition, it is important to emphasize that all inductive (helper) functions of human T cells are contained within the $OKT4^+$ population, although even here the evidence for microheterogeneity of $OKT4^+$ inducer cells is compelling. This evidence stems largely from dissection of the $OKT4^+$ population with the newer monoclonal probe OKT17. This latter antibody also seems to distinguish the radiosensitive and radioresistant helper cells.

The clinical significance of the current analysis of human T cell subsets is clearly worthy of comment. The bottom line probably will be that for straightforward clinical problems there will be straightforward results. Conversely, for complex problems the current probes may yield ambiguous results. An example of a relatively straightforward problem is that of acquired agammaglobulinemia, where at least one defect seems to be an excess of circulating $OKT8^+$ suppressor cells. On the other hand, complex diseases such as diffuse autoimmune states may not be readily assessed by phenotypic analysis of T cell subsets without detailed functional studies of T-T and T-B interactions. It is our optimistic view that future progress with monoclonal probes will address the heterogeneity of human T cells in greater detail and will allow for more precise analysis of human diseases.