Immunoregulatory T Cell Pathways: The Helper T Cell Clone as Target*

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The immune system is faced with the profound task of making appropriate responses which maximally damage foreign invaders while producing only minimum destruction of self tissues. This is not to say that autoimmune damage is necessarily accidental, often a decision is made by the system to accept some self reactivity as a consequence of removing a more immediately harmful foe.[1] As our knowledge increases, we have come to understand that the complexities of immune regulation may make such decision making possible.

Our aim is not to trivialise the decision making processes of the immune system, but to dissect and explore their intracacies. Our efforts have pointed to a central role for the helper T cell as a target for opposing immunoregulatory activities. Down regulation is mediated by T cell interactions resulting in suppression. Contrasuppressor T cell interactions, on the other hand, function to interfere with suppressor T cell signals, leaving immune functions in an "on" mode.

In this paper we will discuss recent studies which employed clones of helper T cells as targets of such immunoregulatory influences. In addition to giving us insights into the mechanisms of action of regulatory T cells, these studies have also revealed some interesting aspects of T cell clones in general. We begin with a consideration of certain regulatory principles ascertained by observations of normal cells and regulatory factors *in vitro*. These principles will then be applied to the modulation of helper T cell clone activity.

Selected "principles" of suppression and Contrasuppression *in vitro*

a. Suppressor effector T cells

Suppressor T cells were first described by Gershon and Kondo[2] who observed that specific unresponsiveness to xenogeneic red blood cells may be transferred bv a population of thymus-dependent (T) cells. This population could be separated from helper T cells on the basis of expression of Ly surface antigens; suppressor cells are Ly-1$^-$, 2$^+$ (Ly-2 cells) while helper T cells are Ly-1$^+$, 2$^-$ (Ly-1 cells). Eardley[3] subsequently generated and demonstrated the action of suppressor cells *in vitro*. Through the investigations of her and others it became apparent that a circuit of T cell subsets interact by produce suppression.[4] The Ly-2 suppressor *effector* cell, the outcome of this circuit, acts upon the helper T cell population to inactivate helper T cell function.[5]

Yamauchi, *et al*,[6] characterised an antigen specific cell free product of activated Ly-2 T cells (Ly-2 TsF) which could suppress helper T cells in a way homologous with that of Ly-2 suppressor effector cells. Using this factor, Flood, *et al.*,[7] delineated the interactions leading to helper cell inactivation. Basically, these are as follows:

1. An interaction of Ly-2 TsF and an I-J$^+$, Ly-1 T cell results in the secretion of an antigen nonspecific molecule bearing an I-J subregion controlled determinant (I-J$^+$ chain). The production of the I-J$^+$ chain requires antigen (that for which the Ly-2 TsF is specific) and an Ia$^+$ non-T cell (probably a macrophage). In addition, the I-J$^+$, Ly-1 T cells and the cells from which the Ly-2 TsF was derived must be matched at I-E.[8]

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This paper is dedicated to the memory and continued influence of Richard K. Gershon, who, for many years, was our mentor, inspiration, and friend. It is also dedicated to his special kind of science, which will never die so long as there is innovation, curiosity, and the bravery to confront the unexpected.

2. The Ly-2 TsF and the newly produced I-J$^+$ chain physically associate (unpublished observations). This interaction is restricted in that the I-J$^+$ chain and the Ly-2 TsF must be derived from cells with the same I-J haplotype.[7]

3. The complex interacts with Ly-1 T helper cells in a manner restricted to genes mapping in or near the Igh-V region. This V_H restriction is determined by the genotype of the I-J$^+$ chain.[7]

Helper T cells, exposed to the complex, become incapable of inducing B cells to secrete immunoglobulin. Whether this inactivation is permanent is not known.

b. Contrasuppressor effector T cells

Contrasuppression is an immunoregulatory T cell activity which functions to interfere with effective suppression.[9] It, too, is produced by the interactions of a specialised circuit of regulatory T cells which results in an Ly-1 effector cell. Unlike helper T cells, the Ly-1 effector cell of the contrasuppressor circuit is I-J$^+$ and adheres to the lectin of *Vicia villosa*. Contrasuppressor effector cells have been identified in cultures of neonatal spleen cell,[10] and in the spleens of animals hyperimmunised to SRBC.[11] Many other sources and instances of contrasuppression are reviewed elsewhere.[12] When helper T cells were exposed to either source of contrasuppression these cells became resistant to subsequent suppressive signals, even after removal of the contrasuppressor cells.[10,11] A molecule (or molecules) in the supernatants of cultured neonatal spleen cells was also found to have a contrasuppressive activity, adhered to a column of anti-I-J antibody, and was capable of rendering helper T cells resistant to suppression. This activity has been tentatively dubbed TcsF.[13]

The basic principles of contrasuppression, then, are that:

1. Contrasuppression is an immunoregulatory activity distinct from T cell help and augmentation.

2. The enhancing effects of contrasuppression operate through interference with active suppression.

3. This interference occurs at the level of the target cell, that is, suppression and contrasuppression operate upon the same cells.

Before proceeding to the suppression and contrasuppression of helper T cell clones, it is important to note that cells other than helper cells may also serve as targets of immunoregulation. These include B cells,[14] antigen presenting cells,[15] and even the cells which induce suppressor cell generation.[5] Nevertheless, control of helper T cells plays a central role in control of immunity. We will next briefly consider the helper T cell clones employed.

The helper T cell clones

Two helper cell clones were used in these preliminary studies.

B6d/D2.B4 is a helper T cell clone derived from BALB/c mice by Dr. C.A. Janeway at Yale University. It is specific for ovalbumin and restricted to the H-2^d haplotype. In the presence of antigen, B6d/D2.B4 proliferates and induces B cell proliferation and antibody secretion. It is not necessary, however, that the T cell and B cell antigens be physically associated (discussed further below). We thank Dr. Janeway for the use of this T cell clone.

C10 is a helper T cell clone derived from C57B1/6 (B6) mice by one of the authors (MH). This clone has the interesting property that it recognises and responds to "self" I-A^b (in the absence of foreign antigen) by proliferating and inducing proliferation and differentiation in B cells. This activity is mediated by the production of a B cell maturation factor (Horowitz,

Table 1 Suppression of cloned BALB/c helper T cells (B6d/D2.B4) by a BALB/c but not a C57B1/6 (B6) T suppressor factor.

	Number of B6d/D2.B4 cells added to $5x10^6$ B cells*	Ly-2 TsF**	Dilution	Assay† (% Control)
a.	$2.5x10^5$	–	–	(100)‡
b.	$2.5x10^5$	Balb/c	1:10	10
	$2.5x10^5$	Balb/c	1:20	53
	$2.5x10^5$	Balb/c	1:40	106
c.	$2.5x10^5$	B6	1:10	75
	$2.5x10^5$	B6	1:20	94
	$2.5x10^5$	B6	1:40	90
a.	$1x10^5$	–	–	(100)☆
b.	$1x10^5$	Balb/c	1:10	0
	$1x10^5$	Balb/c	1:20	22
	$1x10^5$	Balb/c	1:40	172
c.	$1x10^5$	B6	1:10	89
	$1x10^5$	B6	1:20	133
	$1x10^5$	B6	1:40	117

* Under conditions for *in vitro* anti-SRBC response, using OVA-SRBC as antigen. (B cells were anti-Thy-1 + complement treated spleen and made no response alone).

** Ly-2 T cell-derived suppressor factor specific for SRBC from strain shown.

† PFC/culture determined by day 5

‡ 2040 PFC/culture

☆ 720 PFC/culture

et al, manuscript in preparation).

Both T cell clones are dependent upon IL-2 and irradiated (or mitomycin C treated) syngeneic feeder cells. Both have been cloned repeatedly in soft agar.

Suppression of T cell clones with Ly-2 TsF

We begin with a discussion of experiments employing the ovalumin specific BALB/c T cell clone B6d/D2. B4. In the presence of sheep red blood cells (SRBC) conjugated to ovalbumin, this clone can induce B cells to make an anti-SRBC response. In an experiment summarised in Table 1, a plaque forming cell (PFC) response was induced in this manner (group a). When SRBC specific Ly-2 TsF from Balb/c mice was titrated into cultures the response was significantly suppressed (group b). Ly-2 TsF from C57B1/6 mice (B6) did not significantly inhibit the response (group c). This factor was tested and had potent suppressive activity on C57B1/6 spleen cells (data not shown). Thus, as with suppression of normal spleen cells, the suppression of the clone demonstrated genetic restriction. Work is in progress to determine where, in fact, this restriction maps.

In another experiment, B6d/D2. B4 was placed into cultures with B cells (anti-Thy-1 plus complement treated spleen cells) plus or minus antigen. After 5 days the PFC response to SRBC was assessed. Results are shown in Table 2. In the absence of antigen, no PFC response was observed (line a). Addition of SRBC or horse (H) RBC also failed to induce responses (lines b and c). Good anti-SRBC responses were generated when ovalbumin conjugated SRBC (OVA-SRBC) were used as antigen (line d) as in the experiment shown in Table 1. OVA-HRBC failed to induce anti-SRBC responses (line e). However, SRBC plus OVA-HRBC induced a good anti-SRBC response, indicating that the T cell antigen (OVA) and the B cell antigen (SRBC) need not be linked. In other words, the T cell help to B cells did not require an antigen bridge.

The BALB/c Ly-2 T suppressor factors were then employed, one specific for SRBC, one for HRBC. The SRBC specific Ly-2 TsF suppressed only in those cases where the OVA was conjugated to SRBC (compare lines h and j to line i). Similarly, HRBC specific Ly-2 TsF suppressed only when OVA was conjugated to HRBC (compare line 1 to lines k and m).

These results indicate that the Ly-2 TsF required an antigen bridge to inactivate the B6d/D2.B4 clone (lines h, j, and l). It may also be concluded, on the basis of these results, that suppression acted only on the T cells; any other target would have allowed suppression to be seen whenever SRBC were present (as in line i).

Clone C10 was also capable of inducing a PFC response in the presence of SRBC. Again, SRBC specific Ly-2 TsF could suppress the response (Table 3a, group b). When C10 was cultured with Ly-2 TsF plus SRBC for 48 hours, then washed, its ability to help B cells was impaired (Table 3b). Thus, another helper cell clone proved to be susceptible to suppression.

A paradox emerges, however, if we consider the principles of TsF action outlined above. Using Ly-1 T cells, it was demonstrated that a population of I-J$^+$, Ly-1 T cells were required for Ly-2 TsF to be operative. Yet, purified clones of helper T cells are fully susceptible to the action of the suppressor factor.

In an effort to probe this paradox, C10 cells were treated with a monoclonal anti-I-J^b (WF9.40.5) generously supplied by Dr. C. Waltenbaugh. Results are shown in Table 4. Cultures containing C10

Table 2 An antigen bridge is required for suppression of a cloned T helper cell (B6d/D2. B4) but not its ability to help B cells.

	Antigen added to B6d/D2.B4 + B cells*	SRBC specific Balb/c Ly-2 TsF**	HRBC specific BALB/c Ly-2 TsF**	Anti-SRBC assay response
				(PFC/culture)
a)	None	–	–	0
b)	SRBC	–	–	80
c)	HRBC	–	–	200
d)	OVA-SRBC	–	–	2,480†
e)	OVA-HRBC	–	–	280
f)	OVA-HRBC + SRBC	–	–	1,680†
g)	OVA-SRBC + HRBC	–	–	2,480†
				(% Controls)
h)	OVA-SRBC	+	–	22
i)	OVA-HRBC + SRBC	+	–	90
j)	OVA-SRBC + HRBC	+	–	37
k)	OVA-SRBC	–	+	103
l)	OVA-HRBC + SRBC	–	+	17
m)	OVA-SRBC + HRBC	–	+	100

* $2x10^5$ cloned helper cells added to $5x10^6$ anti-Thy-1 + C' treated spleen cells (B cells alone make no response).

** BALB/c Ly-2 T cell derived suppressor factor specific for the antigen shown.

† These values are taken as control (100%) responses for the antigen used.

Table 3a Effect of Ly-2 TsF on cultures of cloned T cells (C10) plus B cells

Number of C 10 cells added to B cells*	B6 Ly-2 TsF (1:10)	Assay (% Control)
$1x10^5$	–	100**
$1x10^5$	+	67
$3x10^4$	–	65
$3x10^4$	+	11
$1x10^4$	–	6
$1x10^4$	+	0.1

*C10 cells were added to $5x10^6$ B cells (Ig^+ spleen cells purified on plastic plates coated with goat anti-mouse Ig) under conditions for an *in vitro* anti-SRBC response.
**63,466 plaques/culture

Table 3b Effect of preculturing cloned T cells with Ly-2 TsF 48 hours before addition to B cells

Number of C 10 cells added to B cells*	C10 cells precultured with Ly-2 TsF**	Assay (% Control)
$1x10^5$	–	100†
$1x10^5$	+	64
$3x10^4$	–	88
$3x10^4$	+	6
$1x10^4$	–	7
$1x10^4$	+	2.5

*C10 cells were added to $5x10^6$ B cells (Ig+ spleen cells purified on plastic plates coated with goat anti-mouse Ig) under conditions for *in vitro* anti-SRBC response.
**before addition to B cells, C10 cells were cultured with SRBC 48 hours in media either in the absence of (–) or in the presence of (+) B6 Ly-2 TsF and then washed prior to addition to the assay population.
†25,000 plaques/culture

Table 4 Treatment of A helper T clone (C10) with a monoclonal anti-I-J antibody plus complement affects its ability to be suppressed with A suppressor effector factor (Ly-2 TsF)

Treatment of C 10 cells added to B cells*	B6 Ly-2 TsF (dilution)	Assay (% Control)
a. C' only	–	100**
b. C' only	1/20	25
C' only	1/40	75
c. Anti-I-J + C'	1/20	87
Anti-I-J + C'	1/40	85

*$1x10^4$ C10 cells, treated with complement (C) or anti-I-J + C, were added to $5x10^6$ B cells (anti-Thy-1 + C treated spleen cells) under conditions for a primary anti-SRBC response.
**1290 plaques/culture

and B cells were readily suppressed by Ly-2 TsF (group b). C10 which had been treated with the antibody, however, was resistant to suppression (group c). In other experiments (not shown) suppression could be restored by the addition of an $I\text{-}J^+$ material from immune Ly-1 T cells as observed previously.[7] This suggests that the $I\text{-}J^+$, Ly-1 T cell required for suppression of a helper population is somehow present in a helper T cell clone. We consider this puzzle further in a later section.

Having suppressed (and inactivated) helper T cell clones, we asked whether a helper cell clone could be susceptible to contrasuppressive influences.

Helper T cell clones as targets of contrasuppression

In the course of studies on suppression of the C10 clone we noted that suppression could be blocked by the addition of contrasuppressor effector cells or supernatants (not shown). It was desirable, however, to rule out any possibility of contaminating augmenting cells or factors which could be interpreted as mediating the contrasuppressive effects. We therefore devised the following experiment.

C10 cells were cultured without feeder cells for 48 hours in media alone (culture a), in a 50% mixture of media plus 5 day supernatants of normal adult spleen cells (culture b), or in a 50% mixture of media plus 5 day culture supernatants of neonatal (7 days old) spleen cells (culture c). Supernatants of normal adult spleen cells sometimes contain an augmenting activity, but do not interfere with suppressor cell function.[13] Neonatal spleen cell supernatants, on the other hand, often contain a potent contrasuppressive activity.[13] The three C10 cultures were washed and added to B cells plus or minus Ly-2 T suppressor factor.

Results are shown in Table 5. C10 cells cultutred in media for 48 hours induced B cells to make an an-

Table 5 Supernatants with contrasuppressive activity render cloned helper cells (C10) resistant to subsequent suppression

	Preculture of C10 cells*	B6 Ly-2 TsF (dilution)	Assay response (% Control)
a)	Media	–	(100)**
		1:10	42
		1:20	67
		1:40	100
b)	50% Adult spleen cell supernatant†	–	238
		1:10	48
		1:20	48
		1:40	29
c)	50% Neonatal spleen cell supernatant☆	–	109
		1:10	128
		1:20	143
		1:40	124

*C10 cells were precultured 48 hours, washed, and added to B cells plus or minus B6 Ly-2 TsF under conditions for primary *in vitro* anti-SRBC response.

**840 PFC/culture (Note: This value is used as 100% throughout this table. Thus, suppression in group b was even more pronounced if compared to response in absence of TsF).

†Culture supernatant of $5x10^6$/ml normal adult spleen cells cultured 5 days. (Mixed 1:1 with fresh tissue culture media).

☆Culture supernatant of $5x10^6$/ml normal neonatal (7d) spleen cells cultured 5 days. (Mixed 1:1 with fresh tissue culture media).

Table 6 "Contrasuppressed" suppression resistant cloned helper cells (C10) have reduced ability to bind an I-J^+ molecule required for function of T suppressor factor

	Supernatant containing the I-J^+ molecule*	Assays** for activity of the I-J^+ molecule I	II
a)	Unabsorbed	+++	+
b)	Absorbed on C10 cells precultured 48 hours in media†	0	0
c)	Absorbed on C10 cells precultured 48 hours in neonatal spleen cell supernatants†	+++	++

*Prepared as previously described (7) and absorbed with SRBC to remove unrelated activities. Factor was used 1:10.

**Assays for I-J^+ chain activity:

I. Ability of supernatant containing I-J^+ molecule to break H-2 restriction of Ly-2 TsF in the appropriate genetic situation (7) i.e., unabsorbed B6 I-J^+ chain allows B6 Ly-2 TsF to suppress CB20 spleen cells

II. Ability of supernatant containing I-J^+ molecule to competitively inhibit Ly-2 TsF activity in appropriate genetic situation (16) (i.e., unabsorbed B6 I-J^+ chain interferes with the action of CB20 Ly-2 TsF on CB20 spleen cells).

†$2x10^6$ C10 cells, precultured as shown for 48 hours and washed, were suspended in 1 ml of I-J^+ chain supernatant for one hour on ice. Factor was then recovered and used in assay system.

ti-SRBC response which was suppressed by addition of Ly-2 TsF (group a). The same cells cultured 48 hours in the supernatant of adult spleen cells induced an elevated response which was equally (or more) suppressible by the Ly-2 TsF (group b). When cells were cultured in the contrasuppressive neonatal supernatants, these cells were rendered completely resistant to the suppressive effects of the Ly-2 TsF (group c).

These results are in accord with earlier observations that contrasuppression functions to render helper T cells relatively resistant to suppressor T cell signals.[10,11]

What happened to the C10 cells to render them resistant to suppression? We had previously observed that the I-J^+ molecule required for Ly-2 TsF function (see "principles") could be absorbed by normal and cloned Ly-1 T cells (unpublished observations). Since binding of this molecule is essential for suppression, we asked whether "contrasuppressed" C10 cells could absorb the I-J^+ molecule.

C10 cells were cultured in media or neonatal supernatants for 48 hours, washed and counted. $2x10^6$ C10 cells from each group were then used to absorb one ml of a supernatant containing the I-J^+ molecule (prepared as described previously).[7] The supernatants, absorbed on ice for 1 hour, were then assayed using two different assays for biological activity of the I-J^+ molecule. These assays have been previously described.[7,16] Regardless of the assay employed, the results clearly indicated that the "contrasuppressed" C10 cells were completely deficient in their ability to bind the I-J^+ molecule required for T cell mediated suppression (see Table 6). Experiments are in progress to investigate the biological nature of this deficiency and to determine whether inability to bind the I-J^+ molecule is, in fact, the final mechanism of contrasuppression.

Thus, the use of cloned helper T cells as targets for suppression and

contrasuppression proves to be a useful strategy for the investigation of these regulatory activities. Concurrently, we are concerned with aspects of the cell biology of such regulation. One must consider, however, the important possibility that helper T cell clones are not exactly representative of helper T cells in general.

What, if anything, is a helper T cell clone?

Helper T cell clones are important tools for studying helper cell function (antigen recognition, B cell activation, etc.). When used as targets for regulation, however, we must be concerned with whether they behave as "normal" helper cells.

We are especially struck with the observation that normal helper cell populations contain cells which do not contribute to T cell help (the I-J$^+$, Ly-1 T cells) but are required for effective suppression by Ly-2 TsF[7] while cloned helper T cells are readily suppressed by this factor. Either the cloned helper cells are simply different (i.e., there is no requirement for the I-J$^+$ cell or the I-J$^+$ molecule it produces) or else the I-J$^+$ cell is contained as a subpopulation in the clone. The initial experiment shown in Table 4 supports the latter.

But if a helper T cell clone contains subpopulations of cells with different functions, then what, if anything, is a clone?

Although derived from a single cell, cloned T cell often have multiple functions.[17] Few attempts have been made to separate these functions to determine whether they correspond to independent subpopulations within the clone. Clones usually have a single antigen specificity, however, which does not change (although it may be lost).

We may propose, therefore, that at a certain stage of T cell development, antigen specificity may be fixed while function remains undetermined (this is analogous to the maturation of B cells). Cells in this state might be capable of unlimited proliferation and differentiation in several directions. We would include the I-J$^+$, Ly-1 T cell as one of the options. Alternatively, the I-J$^+$, Ly-1 T cell required for suppression may represent the helper T cell in one stage of its differentiation. It might, therefore, be possible to "drive" helper cell clones into various modes of activity, to display these diverse functions to greater or lesser extents. Such ideas will continue to be tested.

In any case, these speculations point out that there may be important and independent T cell activities for which uniform T cell clones are simply not possible. Nevertheless, continued studies into the helper T cell and its regulation through the use of helper cell clones should provide useful information about the possibilities inherent in the immune response.

Summary

Clones of helper T cells (T_H) which interact with B cells in primary *in vitro* antibody responses were employed as targets of immunoregulatory T cell factors. Two T cell clones were used, one specific for the protein antigen ovalbumin, the other autoreactive (specific only for I-A^b, with no apparent antigen requirement). Both, under appropriate conditions, help B cells to make anti-sheep red blood cell (SRBC) antibody *In vitro*

Antigen specific T suppressor factors (TsF) were found to inhibit T cell helper activity if a) specific antigen for the TsF is coupled to the appropriate antigen for the T_H, and b) a subpopulation of T cells which react with anti-I-J antibodies is present. Suppression persists when the TsF is removed after 48 hours and the T_H are added to B cells under conditions for a primary *in vitro* immune response.

An antigen non-specific contrasuppressor factor (TcsF) was capable of rendering T_H cells refractory to the inhibitory effects of TsF. Cloned T_H cells, treated for 48 hours in TcsF and washed, were unable to absorb an I-J$^+$ cofactor for suppression. Thus, contrasuppression, which operates to render T_H cells resistant to suppression, may do so by interfering with their ability to bind to a component of suppressor factor.

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