REGULATION OF IgG MEMORY RESPONSES BY HELPER AND SUPPRESSOR T CELLS ACTIVATED BY THE TYPE 2 ANTIGEN, POLYVINYLPYRROLIDONE

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Type 2 antigens such as polyvinylpyrrolidone (PVP),[1] type III pneumococcal polysaccharide (S3), and dinitrophenyl (DNP)-ficoll characteristically elicit antibody responses in mice that consist almost entirely of antibodies of the IgM and IgG3 isotypes (1–4). Type 2 antigens also are generally unable to prime mice to produce IgG1 and IgG2 antibodies after secondary challenge, i.e. they are unable to prime for IgG memory responses (2, 5–8). The inability of these antigens to prime mice for IgG memory responses is presumably due, at least in part, to the fact that type 2 antigens generally do not activate antigen-specific helper T cells (Th), which have been shown (5, 9–14) to be required for the differentiation of B cells to IgG-producing memory B cells. For example, previous studies from this laboratory (5, 6, 14) showed that the type 2 antigen S3 could prime for IgG memory responses only if S3 was coupled to a carrier, horse red blood cells (HRBC), which could activate Th. These activated Th were required for the differentiation of B cells to IgG-producing B memory cells. In subsequent studies using PVP as antigen, it was shown (15, 16) that very low doses (0.0025 μg) of this type 2 antigen could prime mice for IgG memory responses nearly as effectively as a thymus-dependent (TD) form of PVP: PVP coupled to HRBC. By contrast, higher doses of PVP could not induce IgG memory responses; these amounts of PVP actually interferred with the induction of memory cells by PVP-HRBC (15). Consistent with the premise that activation of Th was required to prime B memory cells, it was further shown (15, 16) that the low dose of PVP activated Th, while higher doses did not.

This study further examines the requirements for activation of Th by PVP. The results indicate that higher doses of PVP can activate PVP-specific Th, but that these Th can only be detected when suppressor T cells (Ts) are eliminated. Thus, very low doses of PVP preferentially activate Th, whereas higher doses of PVP activate both Th and Ts, and the activity of the latter cells predominate in whole T cell populations. The implications of these findings for induction of IgG responses to type 2 antigens will be discussed.

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[1] *Abbreviations used in this paper:* C, complement; CY, cyclophosphamide; HRBC, horse red blood cell; PFC, plaque-forming cell; PVP, polyvinylpyrrolidone; S3, type III pneumococcal polysaccharide; TD, thymus dependent; Th, T helper cell; Ts, T suppressor cell.

Materials and Methods

Mice. CAF_1 (BALB/c × A/J F_1) female mice were used for all experiments. They were obtained from The Jackson Laboratories, Bar Harbor, ME and were 8–10 wk old at the time of priming.

Antigens. PVP (360 kilodaltons [kD]) was purchased from Aldrich Chemical Co., Milwaukee, WI. This antigen has been shown to behave as a typical type 2 antigen, in that it elicits antibody that is primarily of the IgM isotype, is immunogenic in both athymic nude and euthymic mice (1, 2), and does not induce antibody responses in CBA/N (*xid*) mice (my unpublished results). A TD form of PVP was prepared as previously described (15) by coupling 360 kD PVP to HRBC.

Priming of Donor Mice. An adoptive transfer system was used for all experiments because this was shown in preliminary experiments to result in higher PVP-specific memory responses than are observed in the intact animal (15). Mice to be used as B cell donors were primed intravenously 2–5 mo before cell transfer with 2×10^8 PVP-HRBC. T cell donors were either not primed (normal T) or were primed 2–3 mo before cell transfer with 0.0025, 0.25, or 25 μg PVP. These doses of PVP are marginally immunogenic (0.0025 μg), optimal (0.25 μg), or supraoptimal (25 μg) in terms of their ability to elicit primary IgM antibody responses in CAF_1 mice (2) (Table II). For some experiments, mice to be used as T cell donors were given 100 mg/kg cyclophosphamide (CY) (Cytoxan, Mead Johnson & Co., Indianapolis, IN) 2 d before priming.

Adoptive Transfer and Secondary Challenge. Mice to be used as recipients of primed cells were irradiated (700 rad) at the ^{60}Co facility at the University of Missouri-Columbia Research Reactor. Within 6 h of irradiation, mice were repopulated with B cells alone ($1–1.4 \times 10^7$ cells/mouse) or with B cells plus $4–6 \times 10^6$ T cells. Mice were immunized immediately after cell transfer with 2×10^8 PVP-HRBC (15). B cells were prepared by treating spleen cells from PVP-HRBC-primed mice with monoclonal anti-Thy-1.2 (HO 13.4) antibody and complement (C), as previously described (5, 14). T cells were obtained from normal or PVP-primed mice by passage through nylon wool, as previously described (5, 14). In some experiments, the nylon wool–nonadherent cells were treated with anti-Lyt-1.2 or anti-Lyt-2.2 and C before transfer (17).

Plaque-forming cell (PFC) Assay. PVP-specific PFC were counted 7 d after challenge of recipient mice using PVP-SRBC as indicator erythrocytes (15). All spleens were also assayed with unconjugated SRBC, and PFC detected with SRBC (usually <800 PFC/spleen) were subtracted from PFC detected with PVP-SRBC. Both IgM and IgG PFC were determined in these experiments as previously described (15).

Results

Activation of Th by PVP Is Antigen-dose–dependent. As shown in Table I, T cells from mice primed with a low dose (0.0025 μg) of PVP are able to provide significant help to B cells from PVP-HRBC-primed mice for production of PVP-specific IgG. In contrast, T cells from normal mice or from mice primed with higher doses (0.25 or 25 μg) of PVP provide little, if any, help to the same B cells. The helper activity of the low-dose PVP–primed T cells is comparable to helper activity provided by T cells from mice primed with PVP-HRBC (16 and my unpublished results). As shown previously (15), T cells generally provide some help to B cells for production of IgM, especially in Exp. 2 of Table I. However, the level of help for IgM is similar whether or not the T cells have been primed with PVP. Therefore, for simplicity, only the PVP-specific IgG responses will be shown in the majority of the studies to be described below. PVP-specific IgG responses are not observed when primed Th are added to B cells from normal mice or mice primed with 0.25 μg PVP, but B cells from mice primed with 0.0025 μg PVP are nearly as effective as B cells from mice primed

TABLE I

Low Doses of PVP Activate Th Required for Production of PVP-specific IgG

Exp.	T cell donors primed with:*	PVP-specific PFC/spleen‡	
		IgM	IgG
1	No T cells	1,007 ± 203	1,207 ± 217
	Nothing	1,259 ± 198	1,717 ± 268
	0.25 μg PVP	1,588 ± 102	1,341 ± 378
	0.0025 μg PVP	1,400 ± 163	6,725 ± 395
2	No T cells	1,163 ± 153	2,113 ± 1,019
	Nothing	3,825 ± 257	5,533 ± 376
	25 μg PVP	3,375 ± 118	2,300 ± 435
	0.0025 μg PVP	2,025 ± 255	18,330 ± 4,859

* Irradiated CAF_1 mice received 1.3×10^7 B cells (anti-Thy-1.2–treated spleen cells) from donors primed with PVP-HRBC. Mice received, in addition, no T cells or 5×10^6 T cells (nylon wool–passed spleen cells) from normal mice or from mice primed 2–3 mo earlier with the indicated amounts of PVP. All mice were immunized with PVP-HRBC.

‡ Mean PVP-specific PFC/spleen ±SEM (4–5 mice/group) determined 7 d after immunization.

TABLE II

Induction of Primary Antibody Responses with Various Amounts of PVP

Antigen dose*	PVP-specific IgM PFC/spleen‡
μg	
0.0025	1,663 ± 91
0.025	5,075 ± 2,384
0.25	23,825 ± 1,348
2.5	19,800 ± 4,183
25	16,875 ± 2,440

* Groups of 4 CAF_1 mice were immunized intraperitoneally with the indicated amounts of PVP.

‡ Mean PFC/spleen ±SEM. IgM PFC/spleen determined 5 d after immunization. IgG PFC were negligible (<1,000 PFC/spleen) in all groups.

with PVP-HRBC (15, 16 and my unpublished results). The low dose of PVP (0.0025 μg) that activates Th and primes memory IgG–producing B cells is only marginally immunogenic for induction of primary IgM antibody responses in CAF_1 mice (Table II). In contrast, 0.25 μg PVP induces optimal primary IgM responses, while 25 μg PVP is supraoptimal but also induces an excellent primary response (Table II). No appreciable IgG is produced after primary immunization with any of these doses of PVP (not shown). Thus PVP-specific Th are activated by doses of PVP that are suboptimal for induction of primary anti-PVP IgM responses.

High Doses of PVP Activate Ts that Suppress PVP-specific IgG Responses. Having shown that 0.25 and 25 μg PVP are unable to activate Th (Table I), the next step was to determine whether T cells from these mice were able to suppress PVP-specific secondary responses. As shown in Fig. 1, recipient mice given

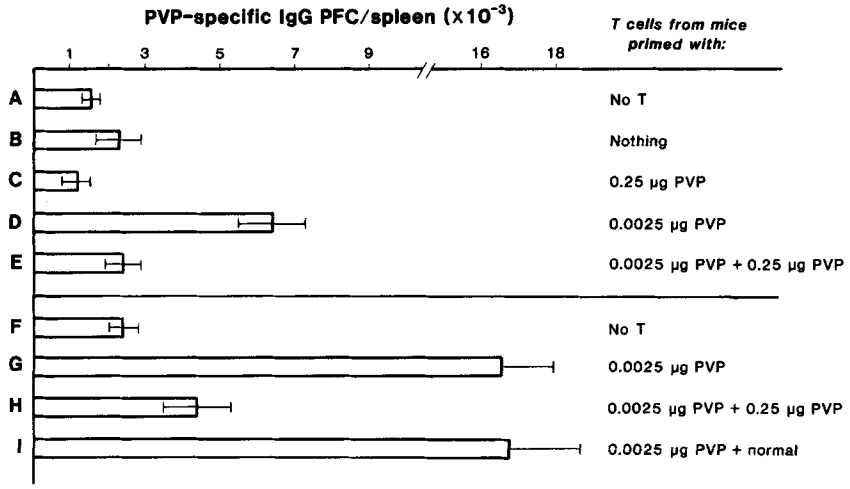

FIGURE 1. Suppression of PVP-specific IgG responses by T cells from mice primed with 0.25 μg PVP. Irradiated CAF_1 mice were repopulated with 1.2×10^7 B cells (anti-Thy-1.2 and C-treated spleen cells) from CAF_1 donors primed 3 mo earlier with PVP-HRBC. Groups *A* and *F* received no additional cells; other groups received B cells plus 5×10^6 T cells (nylon wool–passed spleen cells) from normal CAF_1 mice (*B*) or from CAF_1 mice primed 2 mo earlier with 0.25 or 0.0025 μg PVP. Groups *E*, *H*, and *I* received 5×10^6 of each of the indicated sources of T cells. All mice were immunized with 2×10^8 PVP-HRBC, and PVP-specific PFC were determined 7 d later. Results are expressed as mean IgG PFC/spleen ±SEM of 4–5 mice/group. The mean group IgM PFC responses ranged from 1,125 ± 112 PFC/spleen (*A*) to 1,710 ± 365 PFC/spleen (*E*) in the first experiment, and from 1,713 ± 172 PFC/spleen (*F*) to 3,540 ± 772 PFC/spleen (*I*) in the second experiment.

primed B cells and Th cells from mice primed with 0.0025 μg PVP (Fig. 1, groups D and G) again produced much more PVP-specific IgG than mice given B cells and normal T cells or T cells from mice primed with 0.25 μg PVP (Fig. 1, groups B, C, and F). Mice receiving B cells plus a mixture of low-dose PVP–primed Th and T cells from high-dose PVP–primed mice (Fig. 1, groups E and H) also had much lower IgG responses; T cells from the high-dose–primed mice apparently suppressed the IgG antibody responses. Suppression was dependent on prior priming of the T cell donors with 0.25 μg or more of PVP, since an equivalent number of normal T cells (Fig. 1, group I) or T cells from mice primed with S3 or 0.0025 μg PVP (data not shown) had no effect on the IgG responses. The suppression induced by priming with PVP is long-lasting; in the experiments shown in Fig. 1, cells were from mice primed 2 mo earlier with PVP, and other experiments (not shown) have shown that T cells still have suppressor activity at least 7 mo after priming with 0.25 μg PVP. As stated earlier, the IgM responses of all mice that received T cells, in this and other experiments, varied by less than twofold (also see Table III). Thus, the suppressor cells induced by high doses of PVP selectively suppress PVP-specific IgG responses.

High Doses of PVP Can Activate Th in CY-treated Mice. The results in Table I and Fig. 1 indicate that high amounts of PVP (0.25 or 25 μg) (see Figure 1 and Table III) did not activate detectable PVP-specific Th, but did, apparently, activate Ts, which prevented the production of IgG by primed B cells and PVP-

TABLE III

Abrogation of Ts Activity by CY Pretreatment of PVP-primed T Cell Donors

Group	T cells from mice primed with:*	PVP-specific PFC/spleen‡	
		IgM	IgG
A	No T cells	1,038 ± 180	263 ± 74
B	0.0025 μg PVP	3,580 ± 355	9,660 ± 1,570
C	25 μg PVP	2,425 ± 164	950 ± 155
D	0.0025 μg PVP + 25 μg PVP	2,180 ± 222	1,600 ± 515
E	CY + 25 μg PVP	1,990 ± 640	6,650 ± 1,613
F	0.0025 μg PVP + CY + 25 μg PVP	4,075 ± 805	9,438 ± 1,116

* Irradiated CAF_1 mice received 10^7 B cells from mice primed 3 mo earlier with PVP-HRBC. Group A received no T cells, and Groups B, C, and E received 6×10^6 T cells from donors primed 3 mo earlier with 0.0025 or 25 μg PVP. Groups D and F got 6×10^6 of each of the indicated T cells. CY-treated donors (D–F) received 100 mg/kg CY 2 d before priming with 25 μg PVP. All mice were immunized with PVP-HRBC.

‡ Mean PVP-specific PFC/spleen ±SEM, determined 7 d after immunization (4–5 mice/group).

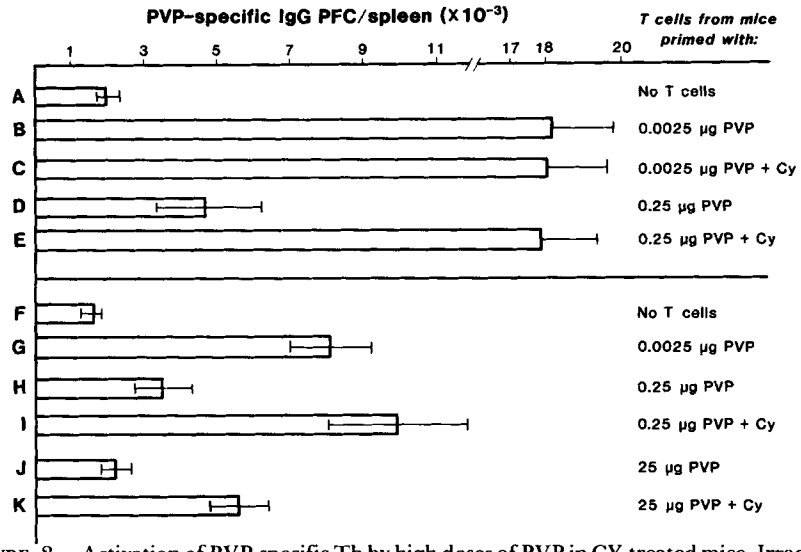

FIGURE 2. Activation of PVP-specific Th by high doses of PVP in CY-treated mice. Irradiated CAF_1 mice were repopulated with 1.2×10^7 B cells (anti-Thy-1.2 and C-treated spleen cells) from mice primed 2.5 mo earlier with 2×10^8 PVP-HRBC. Groups *A* and *F* received no additional cells; all other groups received, in addition, 5×10^6 T cells (nylon wool–passed spleen) from CAF_1 donors primed 3 mo earlier with the indicated amount of PVP. CY-treated donors (*C*, *E*, *I*, and *K*) were given 100 mg/kg CY 2 d before priming with PVP. All mice were immunized with PVP-HRBC, and PVP-specific PFC were determined 7 d later. Results are expressed as mean PVP-specific IgG PFC/spleen ±SEM for 4–5 mice/group. The mean group IgM PFC responses ranged from 2,550 ± 340 PFC/spleen (*A*) to 6,563 ± 2,017 PFC/spleen (*C*) in the first experiment, and from 750 ± 85 PFC/spleen (*F*) to 2,430 ± 253 (*K*) in the second experiment.

specific Th. The question then arose as to whether high amounts of PVP might be able to activate Th that would provide help to primed B cells if the activation of Ts were reduced. Some Ts precursors have been shown (17, 18) to be sensitive to CY. Therefore, mice were given 100 mg/kg CY 2 d before priming with 0.0025, 0.25, or 25 μg PVP. 2–3 mo later, T cells from these mice were assessed for their ability to provide help to PVP-HRBC-primed B cells. As shown in Fig.

2, T cells from low-dose PVP–primed mice again provided help to B cells for IgG responses (Fig. 2, groups B and G), and CY pretreatment did not affect the activity of these Th (Fig. 2, group C). As before, T cells from mice primed with 0.25 or 25 μg PVP had little Th activity (Fig. 2, groups D, H, and J). In contrast, T cells from mice treated with CY before priming with 0.25 μg PVP had as much Th activity as T cells from low-dose PVP–primed mice (Fig. 2, group B vs. group E, and group G vs. group I). CY-treated mice primed with a very high dose (25 μg) of PVP also had significant Th activity (Fig. 2, group K). These results suggest that CY might act to prevent the activation of Ts by high doses of PVP, thereby allowing Th to be activated. To provide more direct evidence for this hypothesis, T cells from both normal and CY-treated mice given 25 μg PVP were assessed for their ability to suppress the responses induced by PVP-primed B cells and Th (Table III). As before, T cells from mice given 25 μg PVP (Table III, group C) provided only marginal help to B cells for IgG responses compared to T cells from low-dose PVP–primed mice (Table III, group B). T cells from 25 μg PVP–primed mice markedly suppressed the IgG response when transferred with low-dose PVP–primed Th (Table III, group D). In contrast, T cells from mice given CY before priming with 25 μg PVP again had significant Th activity (Table III, group E), and these cells did not suppress the IgG response when mixed with low-dose PVP–primed Th (Table III, group F). Thus, treatment of mice with CY before priming with high doses of PVP prevents the activation of Ts by PVP, and results in the activation of PVP-specific Th.

Removal of Lyt-2$^+$ Cells Reveals Th Activity in High-dose PVP–primed T cells. The results described above indicated that PVP-specific Th could be activated by high doses of PVP when mice were given CY at the time of priming to prevent Ts activation. To determine whether Ts activation by high doses of PVP actually prevented priming of Th, or whether the presence of Ts prevented detection of Th activity in these mice, T cells from mice primed 2 mo earlier with either 0.0025 or 0.25 μg PVP were treated with anti-Lyt-1.2 and C or anti-Lyt-2.2 and C before transfer (Fig. 3). The Th activity of low-dose PVP–primed T cells was not affected by treatment with anti-Lyt-2.2 (Fig. 3, group D vs. group B), but was completely eliminated by treatment of these cells with anti-Lyt-1.2 and C (Fig. 3 group C); these Th are Lyt-1$^+$2$^-$ T cells. As before, T cells from mice primed with 0.25 μg PVP had little Th activity (Fig. 3, group E vs. group A). However, when these cells were treated with anti-Lyt-2.2 and C, the remaining (Lyt-1$^+$) T cells had as much Th activity as low-dose PVP–primed T cells (Fig. 3, group F vs. groups B and D). Moreover, as might be expected, these anti-Lyt-2–treated cells no longer suppressed IgG responses when they were mixed with B cells and low-dose PVP–primed Th (data not shown). Thus, 0.25 μg PVP can activate both Th and Ts in normal mice, but Ts activity predominates, so that Th are detected only after Ts are eliminated.

Discussion

The results presented here demonstrate that the type 2 antigen, PVP, can activate Th that are required for the production of PVP-specific IgG by PVP-specific primed B cells. Priming of Th by PVP is most readily accomplished using a very low dose (0.0025 μg) of PVP (Table I), an amount that is only marginally

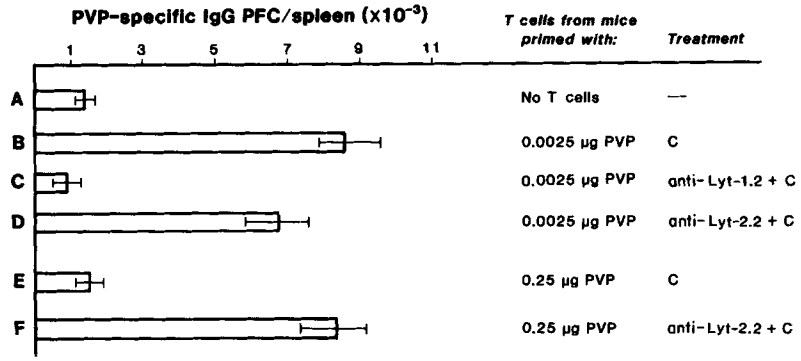

FIGURE 3. Effect of anti-Lyt and C treatment on the activity of T cells from mice primed with 0.0025 or 0.25 μg PVP. Irradiated CAF_1 mice were repopulated with 1.2×10^7 B cells (anti-Thy-1.2 and C–treated spleen) from mice primed 4 mo earlier with PVP-HRBC. Group *A* received no additional cells; groups *B–F* received B cells plus 7×10^6 T cells (nylon wool–passed spleen) from mice primed 3.5 mo earlier with 0.0025 or 0.25 μg PVP. T cells were treated with C alone or with anti-Lyt-1.2 or anti-Lyt-2.2 and C, as indicated. All mice were immunized with PVP-HRBC, and PVP-specific PFC were determined 7 d later. Results are expressed as mean PVP-specific IgG PFC/spleen ±SEM of 8–10 mice/group (results of two separate experiments are pooled). The mean group IgM PFC/spleen ranged from 1,850 ± 240 PFC/spleen (*A*) to 3,910 ± 432 PFC/spleen (*F*).

immunogenic for induction of primary PVP-specific IgM responses (Table II). As previously described (15), however, this low amount of PVP can effectively prime B cells to produce IgG antibody after secondary challenge with PVP-HRBC. In contrast, higher amounts of PVP (0.25 μg), which induce optimal primary anti-PVP (IgM) responses (2) (Table II), do not prime B cells for IgG production in a secondary response to PVP-HRBC (15), and this amount of PVP actually interferes with the development of IgG-producing B memory cells induced by priming with PVP-HRBC (15). Moreover, T cells from mice primed with 0.25 μg or higher amounts of PVP provided only minimal help to primed B cells for IgG production (Table I).

The results of this study also establish that the inability of T cells from mice primed with 0.25 or 25 μg PVP to provide help for IgG production is due to the fact that these amounts of PVP activate T cells that suppress IgG responses when they are transferred together with primed Th and B cells (Fig. 1 and Table III). However, when mice are given CY before priming with high doses of PVP, activation of Ts is prevented (Table III), and T cells from these mice are able to provide excellent help to B cells for the production of IgG (Fig. 2). Moreover, elimination of Ts by treatment of high-dose PVP–primed T cells with anti-Lyt-2.2 and C (Fig. 3) or 1,000-rad irradiation (my unpublished results) just before transfer also eliminates Ts and enables these cells to provide help to B cells for IgG responses. Thus, both low and higher doses of PVP are able to activate PVP-specific Th, although priming with high doses of PVP also results in the activation of Ts, the activity of which predominates and prevents the expression of Th function.

There are several other recent reports in which an apparent absence of antigen-primed Th has been shown to be due to the presence of specific Ts that prevent the expression of Th activity. For example, Jensen et al. (19) found that mice

that are phenotypic nonresponders to pork insulin have pork insulin–specific Ts that predominate and prevent expression of Th activity. Similar observations have also been reported by Pierce et al. (20) for phenotypic nonresponders to GAT (a polymer of glutamic acid, alanine, and tyrosine), by Baxevanis et al. (21) for nonresponders to lactate dehydrogenase B, and by Sercarz et al. (22) for nonresponders to lysozyme. Thus, masking of functional Th by excess Ts may be the mechanism underlying phenotypic nonresponsiveness in at least some *Ir* gene–controlled responses and, as shown here, may also explain why at least some type 2 antigens have not previously been found to activate specific Th.

Previous studies from this as well as other laboratories (2, 5–8, 23, 24) have shown that the so-called thymus-independent or type 2 antigens are unable to prime mice for development of IgG memory responses. The inability of such antigens to prime IgG-producing memory B cells has been attributed to the fact that type 2 antigens are unable to prime Th, which are needed for the differentiation of B cell precursors to IgG-producing B memory cells, since it is well established that TD forms of these same antigens both activate Th and prime memory B cells (5, 14, 15, 23). Moreover, as shown previously (15), a very low dose of the type 2 antigen, PVP, can prime mice for IgG memory responses, and this amount of PVP also activates PVP-specific Th that can interact with primed PVP-specific B cells to result in the production of PVP-specific IgG antibody (15, 16) (Table I). The fact that a low dose of PVP can activate Th, while higher doses do not (Table I), indicates that this type 2 antigen can activate antigen-specific Th, but that these Th can be detected only under defined conditions of immunization, where Ts activation is minimized or eliminated.

These results establish for the first time that commonly employed, i.e., optimally immunogenic amounts of PVP activate Ts, which regulate the function of Th (Fig. 1). The Ts that are activated by immunogenic amounts of PVP appear to selectively suppress the IgG component of the antibody response (Table III), as opposed to PVP-specific Ts activated by tolerogenic forms of PVP, which suppress the IgM response (17, 28). The ability of PVP to activate Ts that mask the activity of the Th needed for IgG production (8–13, 15, 29) may be an explanation for two general features that distinguish immune responses to type 2 antigens from responses to classical TD antigens. These are the production mainly of IgM during the primary response (1–4, 7, 8), and the inability of such antigens to prime for IgG memory responses (2, 5–8, 23, 24). Whether a similar explanation may exist for the inability of other type 2 antigens to elicit or prime for IgG responses is not known. However, other type 2 antigens, such as S3 (25–27) and S6 (G. Milligan, University of Missouri, Columbia, MO, unpublished results) are similar to PVP (15) in that all of these antigens actively interfere with the development and expression of IgG-producing memory B cells induced by TD forms of the same antigens. This suggests that all of these antigens may activate Ts that interfere with the production of IgG, although this has been directly demonstrated only with PVP. Moreover, we have shown that S3 does not prime memory B cells, nor does it activate Th even when low (0.006 μg) doses of S3 are used for priming (6 and my unpublished results). Studies are in progress to determine whether mice primed with S3 might have S3-specific Th that would be detectable if Ts were eliminated.

Whether or not the observations made here with PVP will be found applicable to other type 2 responses, they clearly establish that a type 2 antigen is capable of activating Th, but that immunization with this antigen will be more likely to result in the predominant activation of Ts, which prevent the expression of Th activity needed for IgG antibody production. Although it has previously been suggested (6, 8, 23) that type 2 antigens behave in this manner, this study is the first direct evidence supporting this hypothesis. A major question that remains concerns the mechanisms involved in the induction of dominant suppression by type 2 antigens as compared to TD antigens, which most often induce dominant help, except in some *Ir* gene–controlled responses, as discussed above. These studies are currently in progress.

Summary

T cells from CAF_1 mice immunized with various amounts of the type 2 antigen polyvinylpyrrolidone (PVP) were assessed for their ability to provide help to PVP-specific memory B cells for the production of IgG. Low doses (0.0025 μg) of PVP consistently activated helper T cells (Th), which were required for the production of IgG by primed B cells. In contrast, T cells from mice primed with higher amounts (0.25 or 25 μg) of PVP did not provide significant help to the same B cells for IgG production. Moreover, when mixed with B cells and low-dose PVP–primed Th, T cells from mice primed with 0.25 or 25 μg PVP suppressed PVP-specific IgG, but not IgM antibody responses. The suppressor cells induced by higher amounts of PVP were eliminated either by injecting cyclophosphamide (CY) before priming with PVP, or by treating the primed T cells with anti-Lyt-2.2 and C before transfer. Pretreatment of suppressor T cell (Ts) donors with CY or removal of Lyt-2^+ T cells not only eliminated Ts activity, but also unmasked significant Th activity in the T cells from high-dose PVP–primed mice. Thus, both low and high amounts of PVP can activate Th, although high amounts of PVP also induce Ts, the activity of which predominates in a normal unfractionated T cell population. The amount of PVP (0.0025 μg) that induces dominant help for IgG memory responses was only marginally immunogenic for induction of primary PVP-specific IgM responses, while 0.25 and 25 μg PVP, which induce dominant suppression for IgG memory responses, are optimally immunogenic for primary IgM responses. These results are discussed in the context of the inability of most type 2 antigens to elicit primary IgG responses or to prime memory B cells for production of IgG, responses which are dependent on the function of antigen-specific Th.

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