SELF TOLERANCE AND LOCALIZED AUTOIMMUNITY

Mouse Models of Autoimmune Disease that Suggest Tissue-specific Suppressor T Cells Are Involved In Self Tolerance

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How the immune system recognizes tissue specific antigens as self is an unresolved question. Studies on autoimmune diseases in human and laboratory animals have, however, provided evidence that suppressor T cells are involved in recognition of self (1–9).

Organ-localized autoimmune diseases such as thyroiditis (10), oophoritis (11, 12), gastritis (13), orchitis (8), and prostatitis (14) can be induced in some strains of mice by thymectomy (Tx)[1] at the critical neonatal age without any additional treatment (15). In the present experiments, we studied whether or not active tissue-specific suppressor T cells exist in normal adult mice for the maintenance of self tolerance. We used two mouse models, autoimmune prostatitis and gastritis. The prostate is a suitable organ for such analysis because prostate-specific antigen(s) is probably expressed in adult males, but not in neonatally orchitomized (Orx) males and females (14). Conversely, the stomach is an organ where tissue-specific antigen(s) is expressed from early developmental stages in both males and females. Both prostate and stomach are highly sensitive to development of organ-specific autoimmune disease after immune manipulation of mice, namely, Tx of normal mice and partial reconstitution of T cell function in *nu/nu* mice (16). Our previous studies (8) suggest that two types of immune-competent cells, sensitized and nonsensitized with self antigens, are present in normal mice (8).

Based on this observation, a series of attempts has been made to prevent post-Tx autoimmune prostatitis and gastritis, and to induce these diseases in reconstituted *nu/nu* mice, by injecting different doses of spleen cells from various syngeneic donors. In this way we investigated the relationship between self tolerance and appearance of organ-specific autoimmunity. The present results, together with our previous results, suggest the possibility of the presence of an active tissue-specific suppressor T cell population that is involved in self tolerance.

This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, and from the Ministry of Health and Welfare of Japan.

[1] *Abbreviations used in this paper:* GPC, guinea pig complement; IF, immunofluorescence; Orx, orchidectomy; T_{NAA}, nonactivated autoreactive T cell; T_{NAS}, nonactivated suppressor T cell; T_{PSS}, prostate tissue–specific suppressor T cell, T_{PSA}, prostate tissue–specific autoreactive T cell; T_{SSA}, stomach tissue–specific autoreactive T cell; T_{SSS}, stomach tissue–specific suppressor T cell; Tx, thymectomy.

Materials and Methods

Animals. Hybrids of (C3H/HeMs × 129/J)F_1 (C3.129), heterozygous C3.129 *nu*/+ and homozygous C3.129 *nu*/*nu* mice were used in these experiments. C3.129 *nu*/+ and *nu*/*nu* male mice were produced by mating immunologically reconstituted 129/J *nu*/*nu* males to heterozygous C3H/He *nu*/+ females. Both C3H/He *nu*/+ and 129/J *nu*/+ stocks were made by crossing the *nu* gene from BALB/c *nu*/*nu* to C3H/He and 129/J mice. Both strains of the mice used in this study were from the eighth backcross generation. It was confirmed that both C3H/He *nu*/+ and 129/J *nu*/+ mice accepted a skin graft from syngeneic normal donors for >3 mo. The mice were raised in our laboratory and housed under conventional conditions.

Orx and Tx. Orx was performed on day 0 (Orx-0) under ether anesthesia. Tx was performed on day 3 (Tx-3) by the method described previously (14).

Preparation of Spleen Cell Suspension. Two or three spleens obtained from 3-mo-old normal males, normal females, Orx-0 males, Tx-3 males, or Tx-3 females were used for preparation of cell suspensions by the methods described previously (12). Viable cell concentrations were adjusted to 4×10^5, 4×10^6, and 4×10^7 cells per 0.1 ml in HBSS. Viability of spleen cells was determined by trypan blue dye exclusion; living cell recoveries were of the order of 85–95%.

Treatment of Spleen Cells with Antisera. To exclude T cells or B cells from the inocula, the spleen cell suspensions prepared from normal male, Orx-0, or Tx-3 male mice were incubated with antisera. 10^7 spleen cells in 0.1 ml of Medium 199 (Gibco Laboratories, Grand Island, NY) with 2% FCS were incubated at 4°C with anti-Thy-1.2 antiserum (Searle Diagnostic, United Kingdom; dilution, 1:100) or with anti-Ig antiserum (MBL Ltd., Japan; dilution, 1:100). After 30 min, guinea-pig complement (GPC) (dilution, 1:5) was added. After an additional 30 min incubation at 37°C, the cells were washed with HBSS containing 5% FCS. By these procedures, 35–45% or 60–70% spleen cells were excluded, respectively. Viable cell concentrations were adjusted to 4×10^5, 10^6, 4×10^6, and 10^7 cells/ml in HBSS for inoculation as T or B cell–depleted suspensions.

Spleen Cell Injections. Syngeneic Tx-3, *nu*/*nu* and *nu*/+ male mice received a single i.p. injection of 0.1 ml of spleen cell suspension at 4 d.

Detection of Autoantibody. All animals were killed at 90 d of age. Mice were etherized, then exsanguinated through the axillary artery, and the blood from individual mice was kept. After centrifugation, sera were frozen at −80°C until used. Prostate and glandular stomach of 3-mo-old syngeneic mice were fixed with 2% formalin in PBS, embedded in paraffin at 50°C for 1 h, and then sectioned and used for indirect immunofluorescence (IF) study, according to the methods described previously (12). Sera diluted 20-fold were used to test for autoantibodies.

Histology. Median prostate, glandular stomach, thyroid, testis, adrenal, pancreas, salivary gland, spleen, lymph nodes, liver, kidney, and lung were fixed in Bouin's fixative, embedded in paraffin, sectioned, and stained with H and E for histological examinations.

Skin Graft. Five each of 2-mo-old C3.129 *nu*/*nu* mice that received injections of 4×10^6 spleen cells from normal males, females, or Orx-0 males were transplanted simultaneously with skin grafts from syngeneic and BALB/c donors according to the methods by Manning and Krueger (17). These mice were housed in a conventional room for 14 mo for examination of their health condition.

Results

Development of Autoimmune Prostatitis and Gastritis in Tx-3 Mice. High incidences of autoimmune prostatitis and gastritis were observed in C3.129 mice as a result of Tx-3 without any sensitization with tissue antigens (Table I). Prostatis was characterized by serious disturbances in the secretion of the epithelial cells associated with massive stromal infiltration of mononuclear cells, especially beneath the epithelial cells, and by the presence of circulating autoantibody against epithelial cells of the prostate. Gastritis was characterized by a depletion

TABLE I

Relation between Incidence of Autoimmune Prostatitis and Gastritis Developed in 90-d-old Tx-3 C3.129 Mice

Age at Tx	Mice used (*n*)	Number of mice with:			
		Prostatitis	Gastritis	Prostatitis and/or gastritis	Both prostatitis and gastritis
d					
3	60	42 (70)*	25 (41.7)	51 (85)	16 (26.7)
—	20	0	0	0	0

Mice with both tissue damage and organ specific circulating antibody were counted.

* Numbers in parentheses represent percentage of mice with given diagnosis.

of parietal and chief cells with varying degrees of mononuclear cell infiltration along the thickened muscularis mucosa, and by the presence of circulating autoantibody against parietal cells. The relationship between the incidence of these autoimmune lesions is shown in Table I. 16 out of 60 (26.7%) Tx-3 mice had both lesions. No crossreactivity was detected between each antigen and each circulating autoantibody by indirect IF tests, however. Epididymitis (7 out of 60; 11.7%), sialoadenitis (4 out of 60; 6.7%) and thyroiditis (3 out of 60; 5%) were found in the Tx-3 mice as other inflammatory lesions. No inflammatory lesions were found in non-Tx C3.129 mice.

Prevention of Development of Postthymectomy Autoimmune Prostatitis and Gastritis by Spleen Cells. As shown in Table II, the development of both autoimmune prostatitis and gastritis could be completely prevented if Tx-3 mice received injection of spleen cells from appropriate donors. Injection of 4×10^6 spleen cells prepared from normal male were able to prevent the development of both prostatitis and gastritis, as well as the appearance of organ-specific circulating antibodies in Tx-3 mice. However, when the same dose of spleen cells was prepared from normal females or Orx-0 males, they had no ability to prevent the development of prostatitis, while they were equally competent for the prevention of gastritis. For the prevention of prostatitis, 4×10^7 cells were required. Spleen cells (4×10^7) from Tx-3 males or females could not prevent the development of either lesion; moreover, higher incidences of not only gastritis but also prostatitis were observed.

Effective Dose of Spleen Cells Depleted of Ig^+ Cells for Prevention of the Development of Prostatitis and Gastritis. As shown in Table III, when spleen cells obtained from normal males were depleted of Thy-1.2^+ cells by antiserum treatment, the preventive capacity was completely eliminated, whereas spleen cells of the same source depleted of Ig^+ cells by antiserum treatment were able to prevent the development of both prostatitis and gastritis in Tx-3 mice. The minimum effective dose was 10^6 in both lesions.

Induction of Prostatitis in nu/nu Mice. As shown in Table IV, severe prostatitis (Fig. 1 *a*) accompanied with prostate-specific circulating autoantibody (Fig. 1 *b*) developed in *nu/nu* mice when the mice received injection of 4×10^6 spleen cells obtained from normal female or Orx-0 male donors. A larger dose ($4 \times$

TABLE II

Effects of Injecting Different Doses of Spleen Cells from Different Donors on Prevention of Autoimmune Prostatitis and Gastritis in Tx-3 C3.129 Mice

Cell source	Cells injected	Mice used (n)	Prostatitis		Gastritis	
			Number of mice with lesion*	Effects on prevention	Number of mice with lesion*	Effects on prevention
Normal male	4×10^5	12	8 (66.7)	−	4 (33.3)	−
	4×10^6	15	1 (6.7)	+	0	+
	4×10^7	13	0	+	0	+
Normal female	4×10^5	15	9 (60)	−	6 (40)	−
	4×10^6	15	12 (80)	−	1 (6.7)	+
	4×10^7	14	1 (7.1)	+	0	+
Orx-0 male	4×10^5	10	7 (70)	−	4 (40)	−
	4×10^6	12	9 (75)	−	0	+
	4×10^7	12	0	+	0	+
Tx-3 male	4×10^7	10	9 (90)	−	8 (80)	−
Tx-3 female	4×10^7	15	11 (73.3)	−	13 (86.7)	−

A single dose of viable spleen cells obtained from 3-mo-old syngeneic donors was injected i.p. into Tx-3 mice at day 4, and the recipients were killed at 90 d of age.

* Mice with both tissue damage and organ-specific circulating antibody were counted. Numbers in parentheses represent percentage of mice with lesions.

TABLE III

Effects of Injecting Different Doses of Thy-1.2 or Ig Antigen-free Spleen Cells on Prevention of Autoimmune Prostatitis and Gastritis in Tx-3 C3.129 Mice

Spleen cells treated with	Cells injected	Mice used (n)	Prostatitis		Gastritis	
			Number of mice with lesion*	Effects on prevention	Number of mice with lesion*	Effects on prevention
Anti-Thy-1.2	4×10^5	12	8 (66.7)	−	4 (33.3)	−
	10^6	11	6 (54.5)	−	5 (45.5)	−
	4×10^6	10	8 (80)	−	3 (30)	−
	10^7	10	7 (70)	−	5 (50)	−
Anti-Ig	4×10^5	12	7 (58.3)	−	5 (41.7)	−
	10^6	12	2 (16.7)	+	1 (8.3)	+
	4×10^6	10	0	+	1 (10)	+
	10^7	10	0	+	0	+

Pretreated viable spleen cells obtained from 3-mo-old syngeneic male donors were injected i.p. into Tx-3 mice at day 4, and the recipients were killed at 90 d of age.

* Mice with both tissue damage and organ-specific circulating antibody were counted. Numbers in parentheses represent percentage of mice with lesions.

10^7) of spleen cells from the same donors was not inductive. In contrast no lesion or autoantibody appeared in *nu/nu* mice when the mice received injection of spleen cells from male donors (Fig. 1*c*). Spleen cells from both Tx-3 males and

TABLE IV

Effects of Injecting Two Doses of Spleen Cells from Different Donors on Induction of Autoimmune Prostatitis and Gastritis in C3.129 nu/nu Mice

Donor of spleen cells	Cells injected	Recipients	Mice used (n)	Number of mice with	
				Prostatitis*	Gastritis*
—	—	*nu/nu*	10	0	0
		nu/+	10	0	0
Normal female	4×10^6	*nu/nu*	12	12 (100)	0
		nu/+	10	0	0
	4×10^7	*nu/nu*	11	0	0
		nu/+	10	0	0
Normal male	4×10^6	*nu/nu*	12	0	0
		nu/+	10	0	0
	4×10^7	*nu/nu*	10	0	0
		nu/+	10	0	0
Orx-0 male	4×10^6	*nu/nu*	13	12 (92.3)	0
		nu/+	10	0	0
	4×10^7	*nu/nu*	10	0	0
		nu/+	8	0	0
Tx-3 female	4×10^7	*nu/nu*	9	9 (100)	8 (88.9)
		nu/+	10	0	2 (20)
Tx-3 male	4×10^7	*nu/nu*	10	9 (90)	9 (90)
		nu/+	12	4 (33.3)	1 (8.3)

A single dose of viable spleen cells obtained from 3-mo-old syngeneic donors were injected i.p. into *nu/nu* and *nu/+* mice at day 4, and the recipients were killed at 90 d of age.

* The mice with both tissue damage and organ-specific circulating antibody were counted. Numbers in parentheses represent percentage of animals with given diagnosis.

females were highly effective for induction of prostatitis in *nu/nu* recipients. On the other hand, prostatitis never developed in *nu/+* recipients by this manner except by injection of a large dose (4×10^7) of spleen cells from Tx-3 males with prostatitis. No gastric lesions or autoantibodies against stomach were found when *nu/nu* mice received injection of spleen cells from non-Tx mice (Fig. 2*c*). Development of severe gastritis was limited in *nu/nu* mice that received spleen cells from Tx-3 donors (Fig. 2 *a* and *b*).

Effective Dose of Ig^+ Cell–depleted Spleen Cells for Induction of Prostatitis. When spleen cells from Orx-0 male or Tx-3 male mice were injected into *nu/nu* mice, prostatitis usually could be observed. When the spleen cells from Orx-0 males treated with anti-Thy-1.2 antiserum plus GPC were injected, no autoimmune features of recipient prostates were observed (Table V). On the other hand, the spleen cells treated with anti-Ig antiserum plus GPC still kept the capacity to induce prostatitis but not gastritis. The effective dose of spleen cells was on the order of 10^6. A fourfold-increased number of the spleen cells from the same source was less inductive, and only mild lesions were observed in the recipients. Ig antigen–free spleen cells (10^6–10^7) from Tx-3 males were effective for induction of prostatitis and gastritis.

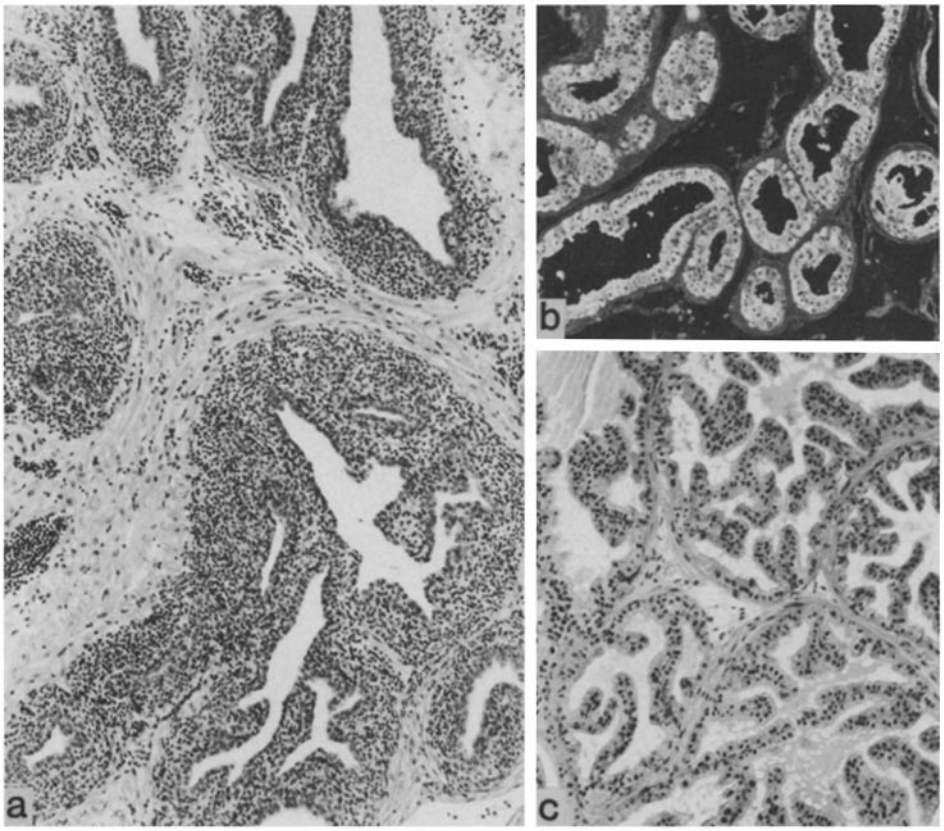

FIGURE 1. Prostatitis and demonstration of the corresponding autoantibody. (*a*) Lesion found in a median prostate of a 3-mo-old C3.129 *nu/nu* mouse that had received a single injection of 4×10^6 spleen cells from Orx-0 males at 4 d. Atrophy of epithelial cells was noticed with severe mononuclear cell infiltration. (*b*) Detection of anti-prostate epithelium antibody in prostatitis by IF. (*c*) Normal features of median prostate observed in a 3-mo-old C3.129 *nu/nu* mouse that received a single injection of 4×10^6 spleen cells from normal males at 4 d. × 110.

In all groups of mice, no lesions were found in other organs examined. T cell areas of the spleen and lymph nodes in all *nu/nu* recipients were satisfactorily reconstituted, except for the recipients that received Thy-1.2 antigen–free spleen cells.

Skin Grafting. All C3.129 *nu/nu* mice that received injections of 4×10^6 spleen cells from normal males, females, or Orx-0 males could accept a skin graft from syngeneic mice, and could reject a skin graft from a different H-2 strain, BALB/c mouse, within 12 d. These mice could live more than 1 yr in a conventional room without any sign of wasting diseases and infection. It would mean that these *nu/nu* recipients have acquired at least minimum immune system for their life. No remarkable lesions were found in these mice, except for severe prostatitis in the *nu/nu* mice that received spleen cells from normal females or Orx-0 males.

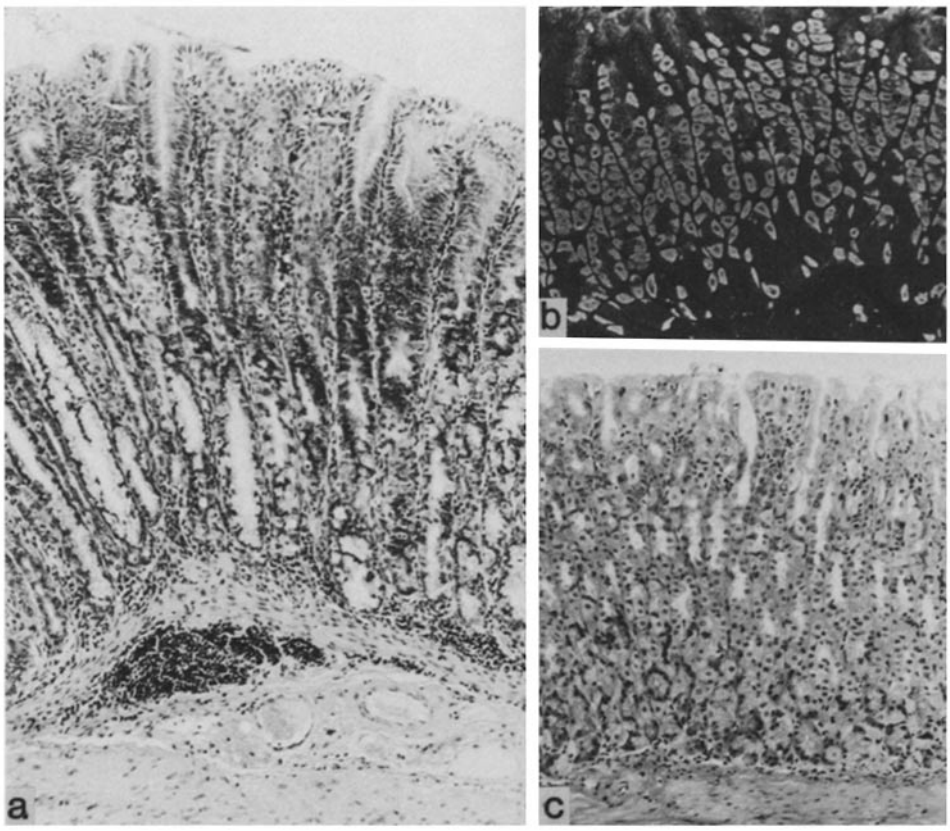

FIGURE 2. Gastritis and demonstration of the corresponding autoantibody. (*a*) Lesion found in the stomach of a 3-mo-old C3.129 *nu/nu* mouse that had received a single injection of 4×10^7 spleen cells from Tx-3 males at 4 d. Depletion of parietal and chief cells and hyperplasia of mucous and endocrine cells were noticed with mononuclear cell infiltration around the muscularis mucosa. (*b*) Detection of anti–parietal cell antibody in gastritis by IF. (*c*) Normal features of stomach observed in a 3-mo-old C3.129 *nu/nu* mouse that received a single injection of 4×10^6 spleen cells from normal females at 4 d. × 110.

Discussion

Prevention or delay of the development of both systemic (18, 19) and organ-localized autoimmune diseases (5, 6, 8, 9) by a single or repeated injections of spleen, lymph node, or thymus cells have been repeatedly reported. Our present experiments confirm these previous reports. Autoimmune prostatitis and gastritis developed with a high incidence in Tx-3 C3.129 mice, and the development of both post-Tx lesions could be prevented completely by a single injection of spleen cells from non-Tx normal mice. Further, it was clearly observed that the capacity to prevent autoimmune prostatitis was higher in the spleen cells from normal males than in those from normal females or Orx-0 males in which no functioning prostatic tissue exists: the effective cell doses were 4×10^6 and 4×10^7, respectively. In contrast, there is no difference in the capacity to prevent gastritis among these three donor groups. Autoimmune prostatitis, but not gastritis, developed in C3.129 *nu/nu* mice when they received a single injection of

TABLE V

Effects of Injecting Different Doses of Thy-1.2 or Ig Antigen-free Spleen Cells on Induction of Autoimmune Prostatitis and Gastritis in C3.129 nu/nu Mice

Donor of spleen cells	Spleen cells treated with:	Cells injected	Mice used (*n*)	Number of mice with:	
				Prostatitis*	Gastritis*
Orx-0 male	Anti-Thy-1.2	10^6	10	0	0
		4×10^6	10	0	0
		10^7	9	0	0
	Anti-Ig	10^6	11	10 (90.9)	0
		4×10^6	10	2 (20)	0
		10^7	10	0	0
Tx-3 male	Anti-Thy-1.2	10^6	9	0	0
		4×10^6	9	0	0
		10^7	10	0	0
	Anti-Ig	10^6	10	10 (100)	9 (90)
		10^7	10	10 (100)	10 (100)

Pretreated viable spleen cells obtained from 3-mo-old syngeneic donors were injected i.p. into *nu/nu* male mice at day 4, and the recipients were killed at 90 d of age.

* The mice with both tissue damage and organ-specific circulating antibody were counted. Numbers in parentheses represent percentage of animals with given diagnosis.

appropriate spleen cells from non-Tx donors. It is interesting that both the number and source of cells are apparently correlated between the effective cells for the prevention and for the induction of prostatitis. That is, a small number of spleen cells (4×10^6) from the Orx-0 donors, which had no ability to prevent post-Tx prostatitis, had the ability to induce lesions of the prostate in *nu/nu* mice. In contrast, the same number of spleen cells from normal male donors could inhibit the development of the lesion in Tx-3 mice, but could not induce prostatitis, and gave a highly immune reconstituted condition in *nu/nu* recipients.

The results of experiments in which spleen cells were used after elimination of Thy-1.2^+ or Ig^+ cells indicate that effective cells for the prevention and the induction of prostatitis were T cells. These results strongly suggest that the normal immune system positively recognizes tissue-specific antigens as self by the regulatory actions of specialized T cells.

Based on the present experiments and on previously reported mouse models (8, 14), we offer this tentative explanation for self-tolerance and localized autoimmunity. In normal mice, subsets of both nonactivated autoreactive T cell (T_{NAA}) and nonactivated suppressor T cell (T_{NAS}) are peripheralized from the thymus. Presumably, in the male, some prostate tissue–specific antigens are normally expressed in the prostatic epithelium with the advance of sexual maturation (14), and immune tolerance against the prostate antigens is possibly maintained by the prostate tissue–specific suppressor T cells (T_{PSS}), which perhaps are continuously generated from a certain fraction of T_{NAS} by crucial stimulation from prostatic antigens. Further, these T_{PSS} have the ability to inhibit the activation of a certain fraction of T_{NAA}, which have the ability to work as prostate tissue–specific autoreactive T cells (T_{PSA}). Such a T_{PSS} population is not present in either normal females or Orx-0 male mice because these mice have no or few antigenic substances of the prostate. In the spleen of non-Tx mice, there exist

many subsets of T cells, including T_{NAS} and T_{NAA}, and presumably, the latter are very dominant compared with the former. Therefore, when male *nu/nu* mice received a small number of spleen cells (4×10^6) from normal female or Orx-0 male donors, T_{PSS} activity was not completely reconstituted due to the presence of the smaller number of T_{NAS} in the inoculum. In contrast, when T_{PSA} were given to *nu/nu* mice, a sufficient number of T_{NAA} were activated by the stimuli of prostate antigens and caused prostatitis. Perhaps a sufficient number of T_{NAS}, which could be activated to T_{PSS}, exist in a large number of spleen cells (4×10^7) prepared from the same donors. In normal males, one could postulate that enough T_{PSS} exist in a smaller number of spleen cells (4×10^6) from normal male mice. Such a conception is strongly supported by the fact that post-Tx prostatitis could be completely prevented by a small number of spleen cells (4×10^6) from normal male donors. Similar results have been reported in the system of post-Tx autoimmune orchitis (8). Therefore, it is understandable that no prostatitis appeared in *nu/nu* mice when the mice received a small number of spleen cells (4×10^6) from normal male mice.

It is possible to assume that T_{NAA} subsets peripheralize earlier than T_{NAS} subsets from the thymus, so that the mice that received Tx-3 have few T_{NAS} subsets (8). Therefore, a high incidence of prostatitis and also gastritis developed not only in Tx-3 mice but also in *nu/nu* mice that received injections of spleen cells from Tx-3 mice. A low incidence of prostatitis and gastritis was found in the *nu/+* recipients when they received a large number of spleen cells (4×10^7) from Tx-3 males. This suggests that T_{PSA} and stomach tissue–specific autoreactive T cells (T_{SSA}) exist in the spleen cells of the donors, and T_{PSS} and stomach tissue–specific suppressor T cells (T_{SSS}) in the *nu/+* recipients could not completely inhibit the activated T_{PSA} and T_{SSA}, respectively. As reported previously (16), oophoritis could be induced in *nu/nu* recipients by injection of spleen cells taken from non-Tx mice. In this case, the mice having an immune system that had not been stimulated by ovarian antigen (normal male and neonatally ovariectomized female mice) were the source of the cells with oophoritis-inducing capacity. In both our previous (16) and present experiments, no gastritis ever developed in *nu/nu* mice after a single injection of spleen cells from non-Tx donors, because of the presence of enough of T_{SSS} in the inocula.

In addition, we described recently (20) the development of severe, multiple, organ-localized autoimmune diseases in T cell function–reconstituted *nu/nu* mice as a result of transplantation of rat thymic rudiments. This model clearly indicates that thymic epithelial/T precursor interaction plays an important role for development and peripheralization of some T cell subsets, and some thymic epithelial abnormalities induce serious unbalance between suppressor and autoreactive T cell populations.

In conclusion, our findings indicate that the normal immune system is provided with a subset of tissue-specific suppressor T cells involved in maintaining self tolerance. Tissue-specific suppressor T cells may develop from a stock of T_{NAS} as a result of stimulation by tissue-specific antigens, and they inhibit the activation of tissue-specific autoreactive T cells from the T_{NNA} subset. In this concept, elimination of the suppressor T cells from the immune system may cause organ-specific autoimmune disease.

Summary

Autoimmune diseases appeared frequently in adults in the prostate and stomach of C3.129 mice after thymectomy on day 3 (Tx-3) without any additional treatment. Lesions of both organs could be completely prevented by a single i.p. injection of spleen cells from syngeneic adult mouse on day 4. For prevention of prostatitis, the most effective cell source was normal males (4×10^6); normal females or Orx-0 males were less effective as the cell source, and higher doses of cells (4×10^7) were needed. In contrast, spleen cells (4×10^6) from these three donors had equivalent capacity for the prevention of gastritis.

Similar autoimmune prostatitis developed at very high frequency when spleen cells (4×10^6) from normal females or Orx-0 males, but not from normal males, were injected i.p. into C3.129 *nu/nu* mice at 4 d. However, no sign of prostatitis was found in *nu/+* recipients. Injection of a larger dose (4×10^7) from the same donors was not effective for induction of prostatitis. Gastritis could not be induced in *nu/nu* mice by this procedure. Injection of spleen cells from Tx-3 males or females was effective for induction of both prostatitis and gastritis in *nu/nu* recipients. It was also shown that a T cell population (Thy-1.2$^+$, Ig$^-$) had the capacity to prevent and to induce autoimmune diseases. These results together strongly suggest a role for active tissue-specific suppressor T cells in self tolerance, and elimination of such T cell populations causes autoimmunity.

We thank Dr. H. L. Hosick, Washington State University, for manuscript preparation, and Mrs. M. Izawa for technical assistance.

Received for publication 18 August 1986.

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