STUDY ON CELLULAR EVENTS IN POSTTHYMECTOMY AUTOIMMUNE OOPHORITIS IN MICE

I. Requirement of Lyt-1 Effector Cells for Oocytes Damage after Adoptive Transfer*

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The thymectomy of some strains of mice during the critical neonatal period (NTx),[1] day 2–4 after birth was reported from this laboratory to induce various organ-specific autoimmune diseases such as oophoritis (1–3), gastritis with megaloblastic anemia (4), thyroiditis (5), orchitis (6), and coagulating gland adenitis of the prostate (6). This experimental model is quite unique in that the diseases develop without any exogeneous sensitization by antigens; furthermore, the spectrum of organs affected, histological features, and the existence of organ-specific autoantibodies are quite similar to those observed in human organ-specific autoimmune diseases. Recently, it was demonstrated (7) that autoimmune oophoritis could be adoptively transferred successfully into syngeneic newborn mice with splenic T cells obtained from NTx mice with oophoritis. The gastritis as well as the oophoritis also could be transferred into syngeneic adult athymic nude mice with resulting organ-specific lesions and circulating autoantibody(ies) (8).

Serological investigation of cell surface antigens on mouse T cells in recent years, particularly Lyt antigens (9, 10), has made it possible to dissect functionally different T cell subpopulations and to characterize T cells at particular differentiation stages. In this report we have attempted to characterize the cell surface antigens and other immunobiological features of the spleen cells responsible for adoptive transfer of the autoimmune oophoritis into newborn mice or athymic nude mice. The findings obtained suggest that cell-mediated immunity quite similar to delayed-type hypersensitivity (DTH) reactions was involved in the destruction of the ovaries in NTx mice.

Materials and Methods

Mice. Congenic mice used for preparation of Lyt antisera (Table I) were kindly provided by Dr. E. A. Boyse, Memorial Sloan-Kettering Cancer Center, New York. A.TH and A.TL

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[1] *Abbreviation used in this paper:* ATS, antithymocyte serum; C, complement; CY, cyclophosphamide; DTH, delayed-type hypersensitivity; HE, hematoxylin and eosin; IF, immunofluorescence; Lyt-1 cells, Lyt-$1^+,23^-$ cells; Lyt-23 cells, Lyt-$1^-,23^+$ cells; NTx, neonatal thymectomy; Tc, cytotoxic T cell; T_{DTH}, effector T cell in delayed-type hypersensitivity; T_H, helper T cell.

TABLE I

Description of Antisera

Antiserum	Autoantibodies absorbed with	Specificity detected	Cytotoxic titer*
AKR/Ms anti-C3H/He Thy‡	A-*Thy-1^a* Thy	Thy-1.2	640–1,280
C3H/An anti-C3H.CE-Lyt-1.2:DS‖ Thy	B6-*Lyt-1^a* Thy	Lyt-1.2	80–160
(C3H/An × B6-*Lyt-2^a*)F$_1$ anti-ERLD	B6-*Lyt-2^a* Thy	Lyt-2.2	160–320
C58 anti-C58.CE-Lyt-3.2:DS Thy	B6-*Lyt-2^a,3^a* Thy	Lyt-3.2	640–1,280
B6 anti-B6-*TL^a* Thy	B6 Thy	TL-1,2,3§	2,560–5,120
		Qa-1§	320–640
A.TH anti-A.TL Spl + LNC	A.TH Thy	Ia^k¶	5,120–10,240

* Titer: the dilution of antisera yielded 50% target cell killing.
‡ Thy, thymocytes; Spl, spleen cells; LNC, lymph node cells; ERLD, radiation-induced leukemia of B6.
§ TL-1,2,3 specificity can be detected when B6-*TL^a* thymocytes were used as target cells. Qa-1 specificity was detected when B6-*TL^a* lymph node cells were used as target cells.
‖ Derived stock.
¶ This antiserum was used to detect Ia antigens on A/J spleen cells coded by I$_{ABJE}$ subregions. 50–60% of cells were lysed at dilutions of 1:10,240. No Ig$^+$ cells remained after treatment with this antiserum and C. This antiserum also showed cytotoxicity against 50–60% of BALB/c spleen cells, probably due to Ia-7 specificity (14), and no Ig$^+$ cells remained after the treatment.

were given by Dr. T. Hamaoka, Osaka University School of Medicine, Osaka, Japan, and A/J was supplied by Dr. K. Moriwaki, Institute for Genetics, Misima, Japan. Other inbred mice were obtained from our breeding colony. BALB/c (*nu/nu*) and their heterozygous littermates were kindly supplied by Dr. K. Suzuki, Institute of Medical Science, University of Tokyo, Tokyo, Japan. Thy-1, Lyt, and Qa-1 phenotypes of A/J and BALB/c are Thy-1.2, Lyt-1.2, 2.2, 3.2, Qa-1$^+$, and Thy-1.2, Lyt-1.2, 2.2, 3.2, Qa-1$^-$, respectively.

Antisera. The antisera against Thy-1, Lyt, Ia, and Qa-1 antigens were prepared in this laboratory according to standard, methods (11–14); Specificity and activity after absorption of autoantibodies are listed in Table I. Anti-thymocyte serum (ATS) was produced by immunizing female New Zealand white rabbits with ASL-1 T cell leukemia cells (15).

Preparation of Cell Suspensions and Bulk Treatment of Cells with Antisera and Complement (C). Bulk treatment of spleen cells with antisera and nontoxic rabbit C was carried out according to the methods of Nakayama et al. (16). Briefly, 1.0–1.5 × 10^7 spleen cells were suspended in 0.2 ml of medium 199 (Gibco Laboratories, Grand Island Biological Co., Grand Island, NY) with 2% fetal calf serum (Gibco Laboratories) containing the appropriate antiserum at a final dilution of 1:7 in the case of anti-Thy-1, anti-Lyt, and anti-Qa-1 treatment or at 1:10 for anti-Ia^k treatment. When cells were treated with goat anti-mouse IgG (Miles-Yeda, Rehovot, Israel), NaN$_3$ was added to the medium at a final concentration of 0.1% (17). After 30 min incubation at 4°C, 0.75 ml of C diluted 1:8 was added, and incubation was continued for another 30 min at 37°C. The cells thus treated were washed twice and then suspended in 0.02 ml for transfer into newborn mice or in 0.2 ml for transfer into adult nude mice.

NTx. Thymus was removed on day 3 (the day of birth as day 0) under ethyl-ether anesthesia as previously described (1, 2).

Preparation of Syngeneic Ovary Homogenates. The preparation of ovary homogenates was carried out as follows: the ovaries of A/J mice, frozen at −70°C, were homogenized and sonicated with Ultra-Turrax sonicator (Ika Werk, Breisgau, Federal Republic of Germany) in Ca^{++}- and Mg^{++}-free Dulbecco's phosphate-buffered saline on ice, and aliquots of 50 mg/0.5 ml were stored at −70°C until used.

Serological and Histological Examination. All mice used in the experiments were bled, and the separated sera were used for the examination of autoantibody against oocytes by testing against cryostat sections of ovaries attached to multi-well slide glasses coated with Fluorogride (Daikin Kogyo Co. Ltd., Osaka, Japan) by indirect immunofluorescence tests (IF) (18). Ovaries and other organs were fixed in 10% formalin solution, embedded in paraffin, sectioned, and then stained with hematoxylin and eosin (HE) for histological examination.

In Vivo Cyclophosphamide (CY) and ATS Treatment and In Vitro Irradiation. NTx A/J mice at 2

mo of age received intraperitoneal injections of 200 mg/kg CY (Shionogi Co. Ltd., Osaka, Japan) 2 d before treatment with ovary homogenates or subcutaneous injection of 0.5 ml of ATS 2 d after treatment with ovary homogenates. Spleen cells were irradiated in vitro just before transfer with the dose of 400 R by a Toshiba X-ray source at a dose rate of 90 rad/min.

Transplantation of Newborn Ovary under Renal Capsule.   Ovaries of newborn mice were transplanted with a fine pasteur pipet into the subcapsular space of the kidney after exposure by retroperitoneal incision. The incision was closed with clips after the operation.

Adoptive Transfer Systems.   Oophoritis was observed in 92% of NTx A/J mice at the age of 2 mo, which was the highest incidence among >10 inbred mouse strains studied thus far (19). NTx A/J mice at 60 d of age received intraperitoneal injections of 0.5 ml syngeneic ovary homogenates and were killed 4 d later. Spleen cells of the mice whose ovaries were completely involuted were used as donors for the adoptive transfer experiment. Spleen cells (4 × 10^7) were treated with various antisera plus C and were injected intraperitoneally into syngeneic newborn A/J mice within 24 h after birth. The mice were killed 7 d after transfer, and the ovaries and other organs were carefully removed for histological examination.

When BALB/c (*nu*/+ or +/+) were thymectomized 3 d after birth, there was a 26% incidence of oophoritis at 2 months of age (8, 19). Spleen cells from NTx BALB/c mice with the disease were treated with antisera and C and injected intravenously into 5–6 week old recipient female BALB/c nude mice. 6 wk after transfer recipient mice were killed, and histological and serological examinations were carried out.

Results

Involution of Affected Ovaries after Treatment with Syngeneic Ovary Homogenates.   In the adoptive transfer experiments, syngeneic ovary homogenates were injected 4 d before killing into 2-mo-old NTx A/J mice. At the time of killing, the total weight of bilateral ovaries removed from NTx mice with or without inoculation of ovary homogenates and from normal control mice was measured (Fig. 1). The mean weight of normal ovaries was 10–13 mg, average 11.4 mg, at 2 mo of age, and that of ovaries from NTx
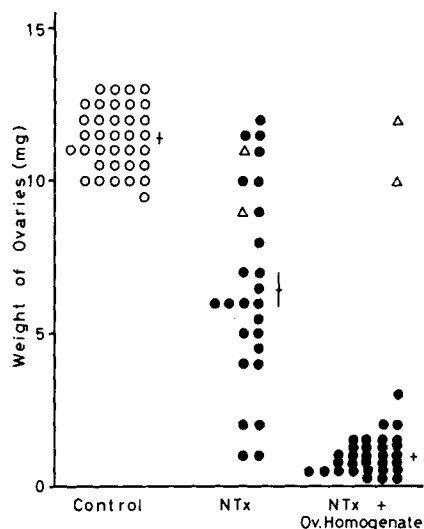

Fig. 1.   Involution of affected ovaries by treatment with syngeneic ovary homogenates. The total weight of bilateral ovaries obtained from the following three groups was measured on a tortion balance: (*a*) 2-mo-old female A/J mice (control), (*b*) NTx mice, and (*c*) NTx mice pretreated with syngeneic ovary homogenates 4 d before killing. O, normal ovaries in control mice; ●, affected ovaries; and △, intact ovaries in NTx mice. Vertical bars show standard errors of the means.

mice with oophoritis ranged from 1 to 10 mg, average 6.4 mg. The ovaries of NTx mice injected with ovary homogenates were acutely involuted and weighed <2 mg, average 0.9 mg. Histologically, ripening follicles and corpora lutea were not observed in the ovaries of NTx mice where infiltration of mononuclear cells was noted, as previously described (3). The ovaries of NTx mice treated with ovary homogenates were completely involuted to a trace mass, and severe infiltration with mononuclear cells was observed.

Lyt-1 Cells but Not Lyt-23 Cells have the Capacity to Transfer Autoimmune Oophoritis into Newborn Mice.   When spleen cells from NTx mice with involuted ovaries after treatment with ovary homogenates were injected intraperitoneally into newborn A/J mice, damage to newborn ovaries could usually be observed within 1–2 d after cell transfer; histological change was distinct when examined at day 7. When the spleen cells treated with anti-Lyt-1 and C were transferred, no pathological alteration of recipient ovaries was observed (Fig. 2 A and B). On the other hand, when the same
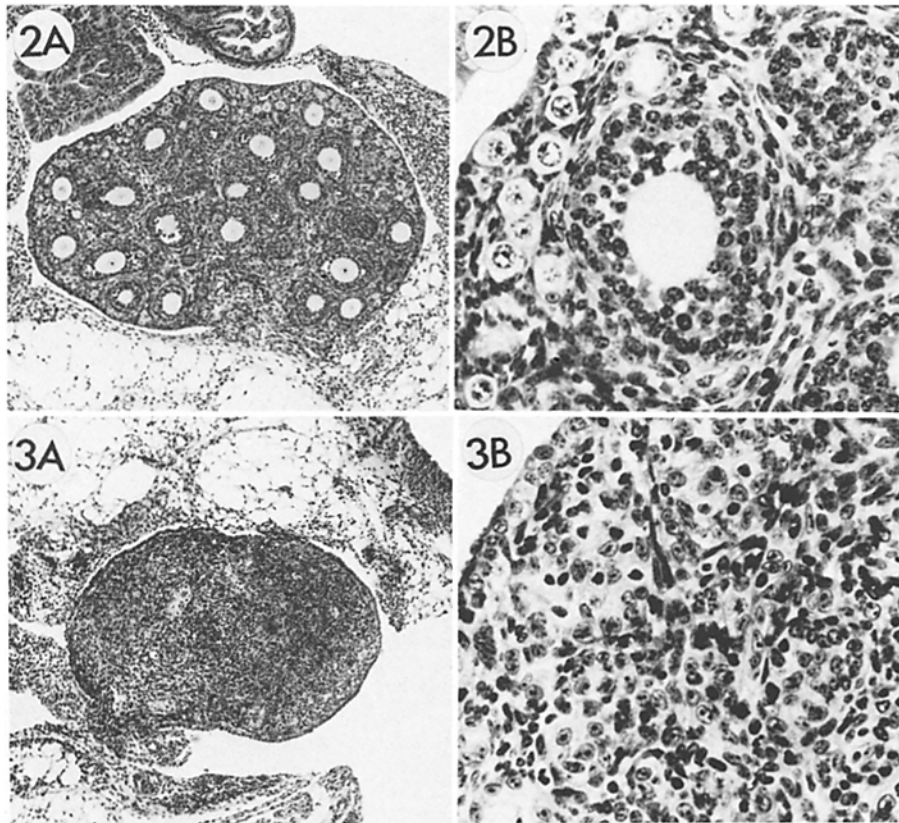
Figs. 2 and 3.   Histology of ovaries of newborn A/J mice injected intraperitoneally with anti-Lyt-1-treated (Fig. 2) or anti-Lyt-2-treated (Fig. 3) spleen cells obtained from NTx mice with oophoritis. As seen in Fig. 2 A and B, many ripening and primordial follicles can be observed when transferred spleen cells were pretreated with anti-Lyt-1 and C. In contrast, the oophoritis is clearly induced as shown in Fig. 3 A and B when spleen cells were pretreated with anti-Lyt-2 and C. Follicular structure is completely absent and massive infiltration with mononuclear cells is noted. (HE stain, Figs. 2 A and 3 A, × 40; Figs. 2 B and 3 B, × 200).

spleen cell population was treated with anti-Lyt-2 or anti-Lyt-3 plus C and the remaining Lyt-1$^+$,23$^-$ cells were transferred into newborn littermates, the recipients' ovaries were completely destroyed with severe infiltration of mononuclear cells as shown in Fig. 3 A and B. Other organs were histologically intact, indicating that the lesion was specific for ovaries. The results of transfer experiments with newborn littermates (Table II) clearly demonstrated that Lyt-1 cells but not Lyt-23 cells had the capacity to transfer oophoritis. Because the treatment with ovary homogenates might have induced Lyt-1 effector cells *de novo*, the Lyt phenotypes of effector spleen cells from untreated NTx mice were studied and were also found to be Lyt-1$^+$,23$^-$ (Table II, experiments 12–14).

Absence of Ia and Qa-1 Antigens on Effector Spleen Cells. When the spleen cells containing the effector T cells were treated with anti-Ia^k serum (A.TH anti-A.TL) plus C and then transferred into newborn A/J mice, the recipient mice developed oophoritis. Expression of Qa-1 antigen on effector T cells was also studied, and it was found that elimination of Qa-1$^+$ cells with anti-Qa-1 and C did not interfere with the capacity to transfer oophoritis (Table III).

No H-2 Restriction in Effector Phase of Adoptive Transfer. To know whether compatibility at the major histocompatibility complex was necessary in our adoptive transfer

TABLE II

Adoptive Transfer of Oophoritis into A/J Newborn Mice: Requirement of Lyt-1$^+$,23$^-$ Cells

Treatment of spleen cells	1 (3)*	2 (3)	3 (4)	4 (3)	5 (4)	6 (4)	7 (3)	8 (4)	9 (3)	10 (4)	11 (3)	12‡ (3)	13‡ (3)	14‡ (3)	Number oophoritis/total
NMS§	++‖	++	++	++	++	++	++	++	++	++	++	+	+	+	14/14
Anti-Lyt-1.2	–	–	+	+	–		–	–	–	–	–	–	–	–	2/14
Anti-Lyt-2.2	++	++	++	++	++	++	++								7/7
Anti-Lyt-3.2								++	++	++	++	+	+	+	7/7
Anti-Lyt-1.2 + anti-Lyt-2.2¶			++		++	+		++		++					5/5

* Number of one littermate in parentheses. Each experiment was performed using newborn female littermates.

‡ Spleen cells used for adoptive transfer were obtained from A/J NTx mice that had not received ovary homogenates.

§ Normal mouse serum.

‖ ++: ovaries of recipient newborn mice were completely destroyed (Fig. 3 A and B). +: more than one-half of the follicles were destroyed, cellular infiltration was observed, but intact follicles and oocytes still remained. –: neither cellular infiltration nor damage of follicles were observed (Fig. 2 A and B).

¶ Mixture of two cell populations: anti-Lyt-1 treated cells and anti-Lyt-2 treated cells.

TABLE III

Adoptive Transfer of Oophoritis into A/J Newborn Mice: Effector Cells Were Ia$^-$ and Qa-1$^-$

Treatment of spleen cells	1 (4)*	2 (3)	3 (5)	4 (3)	5 (3)	6 (4)	7 (4)	Number oophoritis/total
NMS‡	++§	++	++	++	++	++	+	7/7
Anti-Qa-1	++	+	++ +		+	+	–	6/7
Anti-Ia^k	++		++	++	+	++	+	6/6
Anti-Thy-1.2	–	–	–	–		–	–	0/6

* Number of one littermate indicated in parentheses.

§ Normal mouse serum.

‡ ++, +, –: see note to Table II.

TABLE IV

Sensitivity of Effector Cells to ATS, CY, or X Irradiation

Treatment*	Results of transfer		
	−‡	+	++
In vivo ATS 0.5 ml subcutaneously	6	0	0
In vivo cyclophosphamide 200 mg/kg intraperitoneally	0	3	3
In vitro X-ray irradiation 400 rad	0	2	4

* ATS was administered 2 d before killing of NTx A/J mice pretreated with ovarian homogenates. CY was administered 2 d before treatment with the homogenates. X-ray irradiation was performed in vitro against spleen cells from NTx A/J mice pretreated with the homogenates.
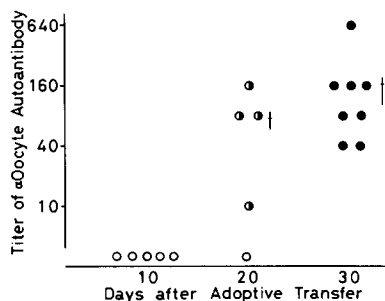

Fig. 4. Transfer of the oophoritis into syngeneic athymic nude mice as demonstrated by auto-antibodies against oocytes and histological examination. Spleen cells (4×10^7) obtained from NTx BALB/c (+/?) mice with oophoritis were injected intravenously into athymic BALB/c nude mice. These mice were killed at 10, 20, and 30 d after transfer and the ovaries of the recipients were histologically examined and titers of antioocyte autoantibody were studied by IF. ○, intact ovary; ◑, damage of more than half of the follicles with loss of oocytes and cellular infiltration were observed, but intact follicles and oocytes still remained; ●, almost all follicles and oocytes were destroyed and severe infiltration of inflammatory cells were observed. Autoantibodies against ooplasm and/or zona pellucidae were detected in the sera of nude mice with damaged ovaries. Vertical bars show the standard errors of the means.

system, the spleen cells from A/J mice with oophoritis were transferred into allogeneic newborn mice (C3H, BALB/c, A.TH, and B6), and their ovaries were examined 4 d after transfer. The result demonstrated that oophoritis could be successfully transferred into all these allogeneic newborn mice including B6 ($H-2^b$), which does not share any common H-2 or I region haplotype with A/J mice. No cell infiltration into other organs or tissues than ovaries was observed, suggesting that the activity of effector cells was specific for ovaries and the damage to oocytes was not due to graft-vs.-host reactions.

Effector Cells Were Sensitive to ATS but Resistant to CY Treatment or In Vitro Irradiation. Spleen cells obtained from NTx mice, injected subcutaneously with 0.5 ml of ATS, could not transfer oophoritis into newborn mice. In contrast the activity of effector cells was not affected by intraperitoneal administration of 200 mg/kg CY (Table IV). Spleen cells, which were X irradiated in vitro with 400 rad, still retained the transfer activity.
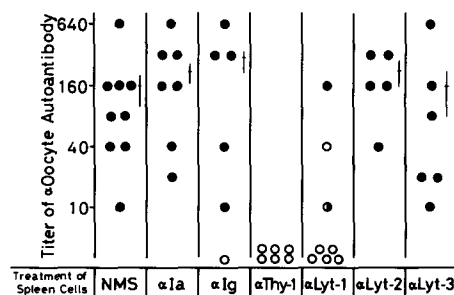
Fig. 5. Lyt-1. cells in NTx BALB/c mice have the capacity to transfer the oophoritis into syngeneic nude mice as demonstrated by titration of autoantibodies and histological examinations. Spleen cells (4 × 10⁷) obtained from NTx BALB/c (+/?) mice with oophoritis were treated with various antisera and C, as described in Materials and Methods. The treated spleen cells were injected intravenously into BALB/c female nude (nu/nu) mice, and these mice were killed at 6 wk after transfer. The histology of the recipient ovaries and titers of anti-oocyte autoantibody in the sera were examined. NMS, normal mouse serum. O, ◐, ●, see legend in Fig. 4. Vertical bars indicate the standard errors of the means.

Adoptive Transfer of Autoimmune Oophoritis into Athymic Nude Mice. Spleen cells from NTx BALB/c (nu/+ or +/+) mice with oophoritis were transferred into syngeneic adult female nude mice. Recipient nude mice were killed at 10-d intervals after the transfer to assess the degree of ovarian injury and the titers of circulating autoantibodies (Fig. 4). The results showed that within 1 mo the oophoritis could be adoptively transferred with accompanying generation of autoantibodies against oocytes. Organs other than ovaries were histologically intact.

Lyt-1 Cells Can Transfer the Oophoritis into Nude Mice. When Thy-1⁺ cells were removed from spleen cells from NTx BALB/c with oophoritis, transfer activity was completely abolished, indicating that the capacity to transfer oophoritis was T cell dependent (Fig. 5). These T cells were further divided according to Lyt phenotype; Lyt-1⁺,23⁻ cells, left after treatment with anti-Lyt-2 or anti-Lyt-3 plus C, could transfer the oophoritis accompanying high titers of circulating anti-oocytes autoantibodies, whereas Lyt-1⁻,23⁺ cells could not.

Newborn Ovaries Transplanted into Athymic Nude Mice with Adoptively Transferred Oophoritis Were Destroyed within 48 h. When ovaries from syngeneic newborn mice were transplanted under the renal capsule of athymic nude mice that had developed oophoritis after transfer of Lyt-1 spleen cells from NTx BALB/c with oophoritis as described above, inflammatory damage of the transplanted ovaries was observed at 24 h after transplantation (Fig. 6 A). At 48 h, transplanted ovaries were completely destroyed and cellular infiltration seemed to have already subsided (not shown). In contrast, when newborn ovaries were transplanted into nude mice that had received anti-Thy-1-treated spleen cells from NTx mice bearing oophoritis, they were histologically intact, as observed in Fig. 6 B.

Discussion

The present experiments of adoptive transfer of postthymectomy autoimmune oophoritis clearly demonstrated that the disease could be transferred into syngeneic newborn mice or athymic nude mice with T cells alone. Furthermore, the Lyt-1 subpopulation was shown to be responsible for successful transfer in both transfer
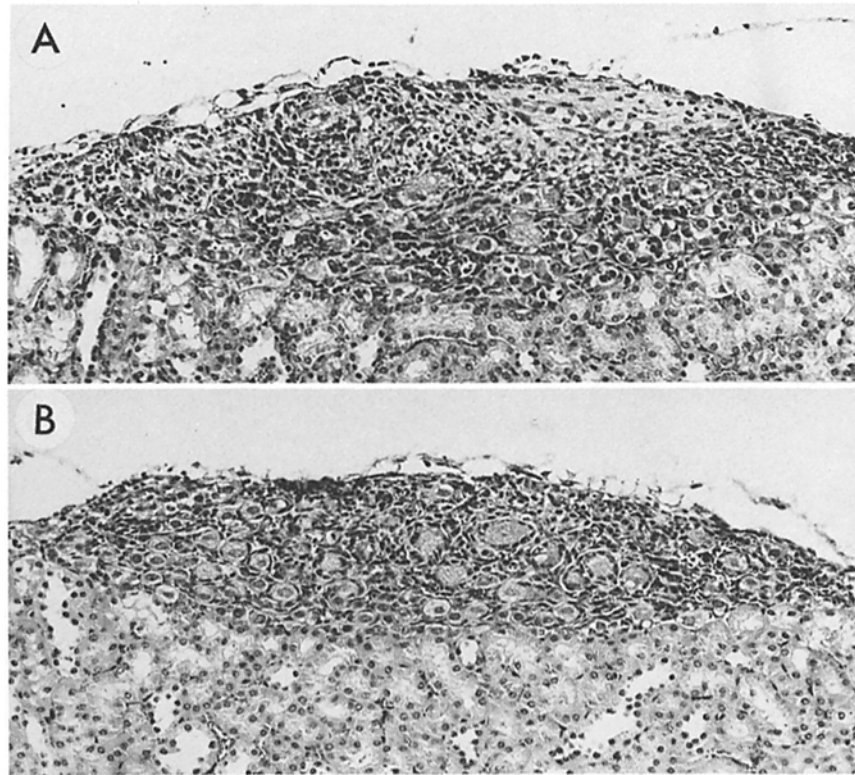
Fig. 6.   Histology of the newborn ovaries transplanted under the kidney capsule of BALB/c nude mice which had received an intravenous injection of Lyt-1 spleen cells from syngeneic (+/?) NTx mice with oophoritis. (A) At 24 h after transplantation, diffuse infiltration of monoclear cells and damage of follicles are noted. On the other hand, newborn ovaries remained intact when they were transplanted into nude mice which had been injected with anti-Thy-1-treated spleen cells and examined at 48 h after transplantation (B) (HE stain, × 200).

systems. The following functions have been so far assigned to Lyt-1 subsets: helper T cell for antibody formation (T_H) (20, 21), effector T cell in DTH (T_{DTH}) (22, 23), amplification of cytotoxic T cells (24), and other regulatory functions (25). From the results of newborn transfer experiments, effector T cells seem to perform their function in a manner similar to T_{DTH} for the following reasons: (a) the Lyt phenotype of the effector cells was Lyt-1$^+$,23$^-$, which was the same as that of T_{DTH} (22, 23) and different from that of cytotoxic T cell, T_C, Lyt-1$^-$,23$^+$, or Lyt-1$^+$,23$^+$(9, 17); (b) the finding that CY treatment and in vitro low dose X-ray irradiation did not interfere with the transfer activity is in agreement with the characteristics so far reported for T_{DTH} (26–29); (c) histological features, such as the remarkable infiltration of mononuclear cells and destruction of follicles in recipient ovaries, suggested that effector T cells and large number of recruited cells, including activated macrophages, might be responsible for the tissue destruction as in DTH (30); (d) the recipient ovaries were affected as early as 1–2 d after spleen cell transfers. This time course of tissue injury was also ascertained by the observation that newborn ovaries transplanted under the renal capsules of nude mice with oophoritis were damaged within 24–48 h after transplan-

tation (Fig. 6); (e) there existed no H-2 restriction in the effector phase of transfer, in contrast to T_C. This result does not contradict the genetic restriction of adoptive transfer in the classical DTH reaction (31, 32) where antigen presentation is required to obtain DTH reaction, which is in contrast to our newborn transfer system where only the direct effects of Lyt-1 cells on target cells could be observed. Recently, several important reports were published concerning the biological function of T_{DTH}. Loveland et al. (33) demonstrated that primed Lyt-1 cells, but not Lyt-1,23 or Lyt-23 T_C, caused skin allograft rejection, and suggested that allografts were rejected mainly by a mechanism similar to DTH. Furthermore, in the H-Y antigen system, a close relationship was demonstrated between Lyt-1 T_{DTH} and in vivo male graft rejection by two groups of investigators (34, 35). Therefore, it is conceivable that T_{DTH}, not T_C, may play an important role in "autograft" rejection in our autoimmune disease model. Recently, the requirement for Lyt-1 cells was reported (36) for the adoptive transfer of experimental autoimmune encephalomyelitis in mice. It should be noted that Waksman (37) had already proposed the hypothesis, in 1959, that pathological lesions underlying a number of organ-specific autoimmune diseases were of the DTH type.

In the other adoptive transfer experiments using nude mice, the Lyt phenotype of the effector cell population was also found to be $Lyt-1^+,23^-$, i.e., Lyt-1 cells alone without committed B cells could transfer the disease with concomitant generation of circulating autoantibodies against oocytes. This result implies that the Lyt-1 population in transferred spleen cells contained T_H to cooperate with virgin B cells in the recipient nude mice for autoantibody formation in addition to effector T cells similar to T_{DTH}. Because B cells competent for forming autoantibodies could not transfer the disease when transferred without committed T cells, Lyt-1 cells seem to be absolutely required probably as direct effector cells. The possibility, however, still remains that autoantibodies produced by the help of transferred T_H might play some role on target organ damage, as destruction of the ovaries of recipient nude mice takes 20–30 d after transfer. One of the approaches to study further the role of T_{DTH} and T_H among Lyt-1 cells is to find new surface antigens that distinguish these two types of T cells. Another approach is to establish clones of effector T cells that can attack target tissue and/or of T_H for autoantibody formation by the aid of T cell growth factors. Ben-Nun et al. (38) have established a T cell line that reacts with basic myelin protein and have successfully induced clinical paralysis in syngeneic rats within 2–3 d after inoculation of cloned T cells. These findings clearly indicated that T cells alone were sufficient to mediate experimental autoimmune encephalomyelitis.

In this study, only the effector cell population involved in autoimmune oophoritis was characterized, but it is probable that effector cells with similar characteristics cause other postthymectomy autoimmune diseases as well. Because in this model, the spectrum of organs affected and immunopathological features of individual diseases are similar to those of human organ-specific autoimmune diseases, it is conceivable that T cell-mediated immunity similar to DTH might play an important role in damaging target organs in human organ-specific autoimmune diseases as well.

Summary

Neonatal thymectomy during the critical period, 2–4 d after birth, can induce various organ-specific autoimmune diseases including oophoritis in A/J mice. The

oophoritis thus induced was passively transferred into neonatal mice by injection of spleen cells obtained from syngeneic donors with the disease. Recipient ovaries were rapidly damaged with remarkable mononuclear cell infiltration and destruction of follicular structures. The phenotype of effector cells responsible for successful adoptive transfer was found to be Thy-1$^+$, Lyt-1$^+$,23$^-$, Ia$^-$, Qa-1$^-$, and was sensitive to anti-thymocyte serum treatment but resistant to cyclophosphamide treatment or in vitro X-ray irradiation. The compatibility between donor and recipient at the major histocompatibility complex was not required for the effector phase of transfer.

The oophoritis induced in BALB/c (nu/+ or +/+) was also shown to be transferred into athymic BALB/c nude mice with resulting ovarian lesion and circulating autoantibodies against oocytes. In this transfer system, the effector cells were also demonstrated to be T cells with the Lyt-1$^+$,23$^-$ phenotype.

Adoptive transfer experiments in both systems revealed that the destruction of ovaries in postthymectomy autoimmune oophoritis was mediated by Lyt-1 T cells. Whether these T cells can be distinguished from other Lyt-1 cells, such as T helper cells and effector T cells in delayed-type hypersensitivity (DTH), is not clear at present, but the results suggest that the effector mechanisms may be closely related to a DTH reaction.

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