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Induction of Granuloma-Dependent Angiotensin-Converting Enzyme and Eosinophil Chemotactic Factor in the Skin of Athymic Nude Mice

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Activities of angiotensin-converting enzyme (ACE), other proteinases, and eosinophil chemotactic factor (ECF-G) are known to be elevated in hepatic hypersensitivity granulomas of thymus intact (nu/+) mice after *Schistosoma mansoni* infection. The enzyme activities also increase, but to a lesser degree in hepatic granulomas of athymic nude (nu/nu) mice, and ECF-G is not detectable. In this study isolated hepatic granulomas from nu/+ mice were grafted into the skin of uninfected nu/nu mice, and changes in those cellular functions were determined to examine whether the newly formed granulomas by recipient nu/nu cells acquire the functional activities as well as the histological appearance of nu/+ granulomas. ACE and ECF-G rapidly disappeared from grafted sites during the first 5 days, corresponding to loss of nu/+ cells from the graft. Reduction in activities of arylsulfatases, lysozyme, and acid phosphatase also occurred, but to a lesser extent. Recovery of ACE and ECF-G activities to the levels seen in nu/+ hepatic granulomas was observed by 14 days after grafting when nu/nu cells had accumulated in the grafts and formed new granulomas. Other enzymes increased to approximately half the levels seen in grafted donor granulomas. Circulating eosinophilia also increased. The findings indicate that nu/nu cells that accumulated in the skin grafts not only morphologically mimicked nu/+ type granulomas but also demonstrated nu/+ levels of cellular function. Analysis of skin granulomas developing in nu/+ mice after grafting of nu/+ hepatic granulomas showed the similar histology and enzymatic changes, whereas the skin sites inoculated with purified schistosome eggs alone caused neither significant histological changes nor elevation of ACE activity.

Key words: hypersensitivity, granulomas, skin, athymic nude mice, biomedical analysis, angiotensin-converting enzyme, eosinophil chemotactic factor

Transplantation of neonatal allogeneic thymus into athymic, nu/nu mice results in replacement of the graft by recipient cells [1,2]. The undifferentiated host T cells

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become "educated" in the process, and this partially restores the cell-mediated immune response of nu/nu mice, including expression of T-cell markers on the plasma membrane. Recently Nishimura et al [3] reported that transplantation of schistosome egg granulomas isolated from livers of *schistosoma mansoni*-infected euthymic, nu/+ mice into nu/nu mouse skin also culminates in the replacement of the graft with recipient nu/nu cells from the bone marrow. Within 1 week after grafting the granulomas became necrotic, while dead eggs and cell debris remained in the hyalinized matrix in the skin. In contrast, tritiated thymidine-labeled cells of nu/nu recipient mice began appearing in the grafted sites and formed new granulomas around the dead eggs within 3 to 4 weeks [3]. Moreover, the recipient cells appeared to have been "educated" by the transplant, because the granulomas that reformed were large, well-organized, and contained 40 to 50% eosinophils, which is characteristic of hepatic schistosome egg granulomas in nu/+ but not in nu/nu mice [4–8]. Transplantation of hepatic granulomas from infected nu/nu mice into skin of nu/nu mice produced small, disorganized granulomas with almost no tissue eosinophilia [9]. The present study was designed to determine if newly formed granulomas in the skin of nu/nu mice show biochemical characteristics of nu/+ granulomas in addition to their morphological appearance.

It has been reported that enzymes, ie, angiotensin-converting enzyme (ACE) [10,11], plasminogen activator [12], neutral proteinase [13], and arylsulfatases [14], are elevated in hepatic granulomas of nu/+ mice. Therefore, we first measured, comparatively, the activities of ACE, lysozyme, arylsulfatase, and acid phosphatase in hepatic granulomas that developed in nu/+ and nu/nu mice with experimental schistosomiasis. The degree of increase in ACE, lysozyme, and arylsulfatase activities was much greater in nu/+ mice than nu/nu mice, suggesting the possibility that these enzyme activities might be associated with the development of nu/+ type granulomas. The enzyme activities were then measured as biochemical parameters in the skin of nu/nu mice at various intervals after grafting nu/+ hepatic granulomas. In addition, the activity of a low molecular weight eosinophil chemotactic factor (ECF-G) was assayed because it increases in the livers of schistosome-infected euthymic [15] but not athymic [16] mice. Furthermore, circulating eosinophil counts were monitored as a measure of systemic involvement. For controls, similar data were obtained after transplantation of nu/+ granulomas into skin of nu/+ mice and after subcutaneous injection of purified eggs in naive, nu/nu mice.

MATERIALS AND METHODS

Animals and Method of Infection

Congenitally athymic nude mice, 6–8 weeks old, and littermate heterozygous mice (25 to 30 gm weight), backcrossed to the BALB/c line purchased from Harlan Sprague-Dawley Co. (Madison, WI) were used. Groups of 15–20 nu/+ and nu/nu mice were infected by subcutaneous injection of 50 cercariae of the Puerto Rican strain of *S mansoni* freshly hatched from snails (*Biomphalaria grabrata*). Nu/nu mice were housed under germ-free conditions and fed sterilized water and chow.

Isolation of Granulomas and Eggs

At 8 weeks after infection, hepatic granulomas were isolated from livers of nu/+ and nu/nu mice by a modification of the method of Moore et al [17]. Granuloma-

tous liver was homogenized gently with 50 ml of Hanks' balanced salt solution supplemented with 100 units/ml of penicillin and 100 μg/ml of streptomycin in a Waring blender at low speed. The homogenate was put into a siliconized glass beaker to allow the granulomas to settle to the bottom. The isolated granulomas were washed several times in the beaker by adding the same solution. Small granulomas from nu/nu mice were isolated similarly, but we usually homogenized three to four livers together to insure the amount of granuloma samples. Eggs were isolated from livers of infected nu/+ mice according to the method of Moore et al [17]. Normal livers were excised from uninfected nu/+ and nu/nu mice and used as controls.

Transplanted Skin Granulomas

Two groups of nu/nu mice were inoculated with either granulomas or eggs isolated from nu/+ mice. A small incision was made with scissors in the suprascapular skin region of the nu/nu mice. The overlying skin was freed from subcutaneous tissues by inserting a metal spatula, and a total of about 1,000 granulomas were inoculated in three different directions of subcutaneous space using the spatula. The wound was then closed with clips. Granulomas from one nu/+ mouse were transplanted into three or four nu/nu mice; about 5,000 purified eggs were inoculated into the skin of each mouse. At 1, 3, 5, 7, 14, 21, 28, and 35 days after transplantation, nu/nu mice were sacrificed by cervical dislocation. The skin lesions were excised, and granulomas were carefully separated from the epidermis and surrounding subcutaneous tissues. All tissues were kept at −70°C until use. As a control, hepatic granulomas isolated from infected nu/+ mice were grafted similarly in the skin of naive nu/+ mice. The skin lesions were excised at 21 days after grafting and used for enzyme assays. Histologically the skin granulomas from nu/+ mice were identical to those from nu/nu mice.

Lysozyme, ACE, Acid Phosphatase Assay

Approximately 50 mg of tissue was homogenized in 1 ml of 20 mM Tris-HCl, pH 7.8, containing 0.25 M sucrose or 55 mM Tris-HCl, pH 7.5, containing 0.15 M NaCl with a Polytron homogenizer. The suspension was used for lysozyme assay. The homogenate was adjusted to 2 ml by adding the same buffer and Triton X-100 to a final concentration of 0.25% (v/v) and stirred at 4°C for 90 min. The homogenate was centrifuged at 1,000g and the supernate used for ACE, acid phosphatase, and arylsulfatase assay. Lysozyme activity was measured at 37°C by the method of Morsky [18]. The reaction was started by adding 0.2 ml *Micrococcus lysodeikticus* suspension (410 mg) in 100 ml of 55 mM phosphate buffer, pH 6.2, containing 0.1% bovine serum albumin and was put into 0.075 ml of the tissue homogenate or egg white lysozyme (Sigma Chemical Co., St. Louis, MO) prediluted in the same buffer. Decrease in absorbance at 500 nm was recorded. The activity was expressed as the egg white lysozyme activity detected in 1 mg tissue protein. ACE activity was measured with a method established by Hara et al [11]. In this assay, 20 μl of enzyme solution was added to 0.23 ml of 0.1 M phosphate buffer, pH 8.3, 5.5 mM hippuryl-histidyl-leucine, and 2.5% n-butanol. After incubation at 37°C for 10 min, released histidyl-leucine was measured fluorometrically. Acid phosphatase activity was measured by the method of Smith and Whitby [19] with disodium p-nitrophenyl phosphate, while arylsulfatase activity was assayed by the method of Worwood et al [20]. One unit of ACE, acid phosphatase, and arylsulfatase was defined as the amount of

enzyme that hydrolyzed 1 μmole of each substrate per minute at 37°C. Protein concentration was determined by the method of Lowry et al [21] using bovine serum albumin as the standard.

ECF-G Assay

Granulomas (100 mg) from nu/+ mice before transplantation and skin granulomas (100 mg) developed in nu/nu mice were homogenized in 1 ml of cold saline with a glass homogenizer. The supernate was taken after centrifugation at 20,000 g for 15 min and dialyzed overnight against 50 ml of HBSS using Spectrapor 3 membrane (molecular cut off at 3,500). ECF-G activity was measured by the method of Tsuda et al [15] using a Boyden chamber. Peritoneal eosinophils migrating through a 5 μm pore filter were counted, and ECF-G activity was expressed as mean numbers counted in ten fields under ×400 magnification.

Peripheral Blood Eosinophil Count

Free-flowing blood from femoral vessels was aspirated into white cell pipettes and diluted with Discombe's solution (5 parts 1% eosin, 5 parts acetone, and 90 parts water). The cells were counted in a Speirs-Levy chamber under a light microscope.

Statistical Method

Statistical analysis of the data was performed using the Student t test. Differences were considered significant at values lower than or equal to 0.05.

RESULTS

Enzyme and ECF-G Activity in Hepatic Granulomas

All activities in livers of uninfected nu/+ and nu/nu mice were almost identical. At 8 weeks after infection the levels of ACE, lysozyme, and arylsulfatases in hepatic granulomas of nu/+ mice were approximately a 740-, 13- and 10-fold higher, respectively, than those in normal livers (Table I). Acid phosphatase activity was essentially the same. Activities of the four enzymes in granulomas of nu/nu mice are also compared to activities in normal livers (Table I). Activities of ACE and arylsulfatase were also increased in the granulomas of nu/nu mice compared to normal,

TABLE I. Enzyme Activities in Extracts of Granulomas and Normal Liver Prepared From nu/+ and nu/nu Mice

	nu/+ Mice (N = 5)		nu/nu Mice (N = 5)	
Enzyme	Granulomas	Normal liver	Granulomas	Normal liver
ACE (mU/mg protein)	74.59 ± 11.71*	0.09 ± 0.08	2.45 ± 1.43	0.09 ± 0.03
Lysozyme (μg egg white/mg protein)	9.54 ± 1.91*	0.71 ± 0.16	0.78 ± 0.16	0.91 ± 0.81
Arysulfatases (mU/mg protein)	50.15 ± 6.16*	4.67 ± 0.07	11.16 ± 3.78	6.46 ± 0.05
Acid phosphatase (mU/mg protein)	0.75 ± 0.13	0.68 ± 0.16	0.75 ± 0.09	0.73 ± 0.03

*The P value was calculated for each enzyme by comparing activities in nu/nu mouse granulomas vs nu/+ mouse granulomas at 8 weeks after infection. Statistically significant. $P < 0.001$.

although the increase was limited to a 27-fold for ACE and 1.7-fold for arylsulfatase. There was no change in acid phosphatase, and lysozyme activity decreased. ECF-G activity was detectable in isolated hepatic granulomas of nu/+ mice, as found by Tsuda et al [15], but not in granulomas of nu/nu mice as Isoda and Epstein [16] reported.

Enzyme Activity in Skin Lesions

Within 24 hr after grafting nu/+ hepatic granulomas, ACE activity (Fig. 1a) decreased significantly ($P < 0.001$) to 8.75 ± 1.98 mU/mg protein. The value further decreased by day 3 (6.65 ± 0.76 mU/mg protein) and day 5 (4.08 ± 0.29 mU/mg protein) after grafting. However, a return of enzyme activity was seen by day 7, and by day 14 it had reached 30.92 ± 6.68 mU/mg protein. The activities found by day 21 (82.97 ± 16.86 mU/mg protein) and day 28 (89.64 ± 12.80 mU/mg protein) were as high as that found in hepatic granulomas of nu/+ mice before transplantation.

The pattern of initial decline and subsequent increase in activity was seen for the other three enzymes tested, although the degree and time required for disappearance and restoration of the activities of lysozyme, arylsulfatases, and acid phosphatase differed from ACE. Lysozyme activity appeared to increase on day 1 and then decrease by day 5 (15.30 ± 0.44 μg egg white/mg protein and 5.41 ± 0.48 μg egg white/mg protein, respectively). The highest enzyme activity (9.64 ± 2.78 μg egg white/mg protein) was seen by day 21, which is the activity level found in nu/+

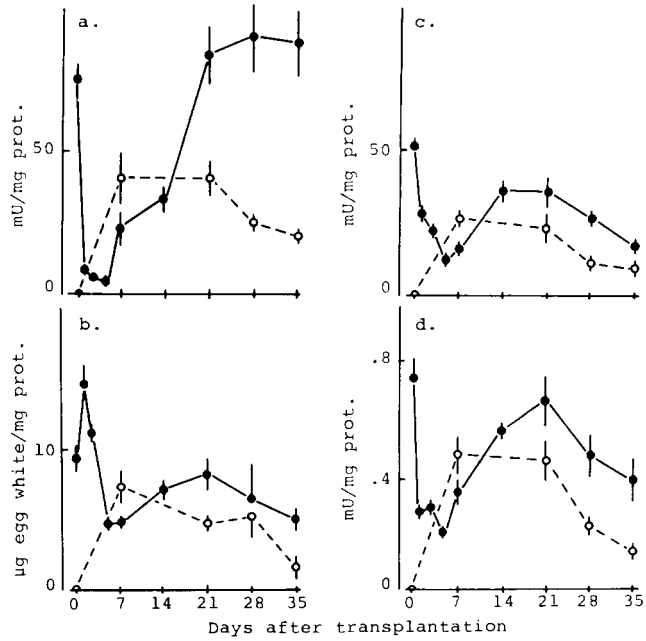

Fig. 1. Activity of angiotensin-converting enzyme (**a**), lysozyme (**b**), arylsulfatases (**c**), and acid phosphatase (**d**) in skin lesions of nu/nu mice at different time intervals after grafting hepatic granulomas isolated from nu/+ mice (●). The activities were compared to those in skin lesions after injection of parasite eggs alone (○). Each point represents the mean ± standard error of three to ten mice. Day 0 is derived from hepatic granulomas or eggs before grafting.

hepatic granulomas. Arylsulfatases (Fig. 1c) and acid phosphatase (Fig. 1d) were reduced to 12.78 ± 3.18 and 0.20 ± 0.01 mU/mg protein, respectively, by day 5; the activities gradually increased but not to the levels measured in nu/+ granulomas. Arylsulfatases, lysozyme, and acid phosphatase activities were further decreased by day 28; however, ACE activity was retained (89.64 ± 12.80, 87.27 ± 20.45 mU/mg protein).

Table II compares enzyme activities detected in the granulomas developed in the skin of nu/nu with those in nu/+ mice. As they showed cross similarity in histological appearance, the enzyme activities were almost identical. The enzyme activity detected in the skin sites where parasite eggs alone were inoculated differed from the granuloma sites (Fig. 1a–1d). All enzyme activities were elevated at day 7 after injection: ACE, 42.07 ± 12.05; arylsulfatases, 27.47 ± 6.64; acid phosphatase, 0.48 ± 0.17; and lysozyme, 8.28 ± 3.20 μg egg white/mg protein. These levels were about half of the activities in hepatic granulomas from nu/+ mice. The enzyme levels stayed unchanged up to 21 days after egg inoculation and decreased by day 35. Histological studies by others [22,23] and us [3] have shown that organized granulomatous tissue reactions do not appear in the skin sites of uninfected mice injected with egg alone. Instead, there is an early, mixed acute and foreign body response that subsides fairly quickly. The striking increase of ACE activity measured in the granuloma skin sites on days 21 to 35 was not detected with egg inoculation at any time interval.

ECF-G Activity in Skin Transplants

The activity (Fig. 2) was gradually reduced after transplantation, and almost no activity was detectable by day 5. Recovery occurred by day 7, and the same level of activity detected in nu/+ granulomas was seen by day 14. However, the activity then gradually decreased. This was not seen after injection into skin of purified eggs only.

Peripheral Eosinophil Counts

Eosinophil counts of noninfected nu/nu mice were 20.0 + 20.5/mm^3 (0.7% of the total white cell counts) (Table III). Grafting nu/+ granulomas caused an increase in the counts, reaching 124.4 ± 42.9 (7.4% of the total white cell count) by day 3. The counts then reached a second peak (444.6 ± 369.6; 10.2% of the total white cell count) by day 14, and this dropped gradually over the next 2 weeks.

TABLE II. Enzyme Activities in Extracts of Skin Granulomas Developed in nu/nu and nu/+ mice 3 Weeks After Grafting nu/+ Hepatic Granulomas

Enzyme	nu/nu Mice (N = 10)	nu/+ Mice (N = 9)
ACE (mU/mg protein)	82.97 ± 16.86	85.19 ± 23.57
Lysozyme (μg egg white/mg protein)	8.03 ± 1.38	6.20 ± 0.77
Arylsulfatase	33.11 ± 10.22	33.07 ± 5.63
Acid phosphatase (mU/mg protein)	0.66 ± 0.15	0.79 ± 0.14

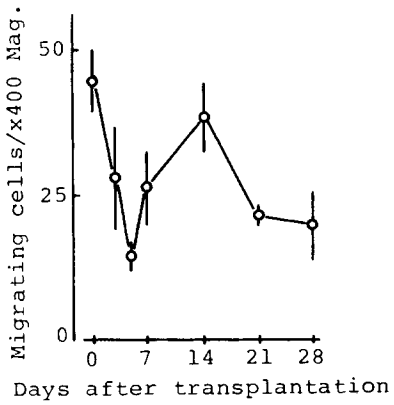

Fig. 2. Comparison of ECF-G activity in the subcutaneous lesions of nu/nu mice at different time intervals after grafting isolated hepatic granulomas of nu/+ mice. Each point represents the mean ± standard error of three to five mice.

TABLE III. Peripheral Blood Eosinophil Counts in nu/nu Mice After Transplantation of Hepatic Granulomas Into Skin

		Eosinophils		
Days postgrafting	No. of mice	Absolute number in mm^3	%[a]	P value[b]
0	4	20.0 ± 20.5	0.7 ± 0.7	—
1	5	42.2 ± 31.9	1.9 ± 1.9	NS
3	5	124.4 ± 42.9	7.4 ± 2.3	< 0.05
5	5	97.6 ± 70.1	4.2 ± 3.2	NS
7	5	99.8 ± 80.3	3.1 ± 2.2	NS
14	5	444.6 ± 369.6	10.2 ± 6.4	< 0.01
21	5	213.4 ± 96.7	7.5 ± 4.4	< 0.05
28	3	66.3 ± 48.0	2.6 ± 1.2	NS

[a]Eosinophil percentage of total white blood cell count.
[b]The P value was calculated by comparing absolute number on each day vs day 0. NS, not significant.

DISCUSSION

Elevated ACE activity was detected in hepatic granulomas that developed in nu/+ mice 8 weeks after *S mansoni* infection as reported by Weinstock et al [10] and Hara et al [11]. ACE has been detected in macrophages in vitro [24,25] epithelioid cells, and giant cells of sarcoid granulomas [26]. Induction of ACE activity has been considered to be a T cell-dependent phenomenon [27–29], although Krulewitz et al [30] reported that granulomas of nu/nu mice contained higher ACE activity than those of nu/+ mice. In the present study small granulomas isolated from livers of nu/nu mice after 8 weeks of infection showed ACE activity lower than that in nu/+ mice but significantly ($P < 0.01$) higher than in normal liver of both nu/+ and nu/nu mice, indicating that granulomatous tissue reaction stimulates ACE activity without significant T-lymphocyte stimuli, but to a lesser degree than in the nu/+ mice. Elevation of arylsulfatase activity in granulomas previously reported [14] in nu/+ mice was confirmed in the presesnt study. As seen for ACE, this enzyme activity in granulomas of nu/nu mice was higher ($P < 0.01$) than in normal liver, but significantly ($P < 0.001$) lower than in nu/+ granulomas. Production of this enzyme is

also T cell-independent, but granuloma enlargment results in amplification of enzyme production. On the other hand, lysozyme activity was increased only in nu/+ granulomas, suggesting T cell dependency in induction of this enzyme. Acid phosphatase did not seem to have any correlation with T-cell function. Hara et al [31] found that this enzyme activity is elevated in skin conditions that are not T cell-dependent, such as nevi and foreign body granulomas. ECF-G production in granulomas in the present study was also consistent with previous findings [15,16], and we interpreted this to mean that T-cell function increases its production, while only minimal amounts are produced in nu/nu granulomas.

All enzyme activities in skin lesions were reduced in the transplants during the first 5 days postgrafting, the period when Nishimura et al [3] observed, histologically, the disappearance of grafted nu/+ mouse macrophages and epithelioid cells but an accumulation of inflammatory cells from the nu/nu host. The initial decline in enzyme activity was most striking for ACE, suggesting that this enzyme is derived primarily from nu/+ cells in granulomas. In contrast, arylsulfatases and acid phosphatase were reduced only to about one-third, indicating that nu/nu inflammatory cells also are capable of producing these enzymes. Lysozyme activity was elevated even at day 1. Neutrophil and mononuclear phagocytes, which appear in the skin sites, may be responsible for the elevation, because they contain lysozyme activity [32,33]. The findings with ECF-G were similar to reported enzyme changes produced by granulomatous macrophages, as it also disappeared from the transplant during this time. Recovery of enzyme activity and ECF-G production was seen as nu/nu macrophages began to reform granulomas. The activities were as high as the levels seen in nu/+ hepatic granulomas and in the skin of nu/+ mice grafted with hepatic granulomas, supporting the view that nu/nu host cells had acquired the functional activity expected of nu/+ cells. Furthermore, inoculation of purified schistosome eggs into the skin of uninfected nu/nu mice resulted in an early, modest elevation of arylsulfatase, acid phosphatase, and lysozyme activities but to lesser degrees than seen in granulomatous lesions, and the activities declined during the 28 day experimental period.

These observations indicate that the inflammatory cells that accumulate about purified eggs in skin are functionally different from those that reform granulomas around the egg-granuloma transplants. In keeping with the idea that purified eggs alone elicit a mild foreign body response, the ACE level followed a similar pattern of activity and did not give a high level of activity at 21 days as was observed with granuloma transplants.

The restoration of nu/+ cell type function was not limited to the grafted microenvironment, but also appeared as circulating eosinophilia, which is generally a T cell-dependent function [34,35]. The mechanisms by which nu/nu cells acquired enzyme induction remain to be investigated. However, a similar functional adaptation has been reported in nu/nu mouse macrophages after thymus transplantation [1,2], chronic antigenic stimulation [36], and injection of splenic cells [37]. Two possibilities exist: 1) the graft contained active T lymphocytes, which directly stimulated nu/nu macrophages function; or 2) T-cell precursors known to exist in nu/nu mice [1,38] are stimulated to differentiate by factors in the transplant. Studies are in progress to elucidate the systemic effects caused by the granuloma grafts. It should be emphasized that injection of isolated eggs alone does not lead to reconstituted granulomas [3].

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