Production of Autoimmune Gastric Hyperplasia in Mice by the Transfer of Spleen Cells from Thymectomized Donors

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ABSTRACT

Previous work showed that mice that had been thymectomized at 3 days of age tended, in later life, to develop a hyperplastic autoimmune gastritis and were also hypersusceptible to sarcogenesis by low dosages of 3-methylcholanthrene. In the present work, it was found that the hyperplastic autoimmune gastritis could be transferred with great efficiency with spleen cells obtained from 3-mo-old donors that had been thymectomized at 3 days of age, but which had not, at the time of transfer, themselves developed overt disease. The recipients were 1-mo-old syngeneic mice that had been made receptive by thymectomy during the first day of life, a procedure that does not, of itself, cause autoimmune disease. The high efficiency of the transfer suggests that, during the transfer process, effector cells may have been differentially favored as compared with the suppressor cells that, in normal animals, supposedly prevent autoimmunity. The practicality of the transfer technique should permit an investigation of the cellular basis of the autoimmunity and the associated increased susceptibility to low-dose hydrocarbon sarcogenesis.

INTRODUCTION

Thymectomy at 3 days of age, but not at birth or after about 5 days of age, produces appreciable incidences, in later life, of a variety of localized autoimmune lesions, infiltrated with lymphocytes, such as oophoritis, thyroiditis, gastritis, etc. (1). Some of the lesions are more hyperplastic than destructive; the gastritis, for example (2), produces so much hyperplasia that it is easily palpable through the abdominal wall and is easily recognizable without microscopic examination (photomicrographs of the histological sections were published in Ref. 2). The actual incidences and the spectrum of lesions are a function of the strain of mouse (1).

The hyperplasia, in the case of oophoritis, has occasionally progressed to neoplasia (3), and it has now been shown that 3-day thymectomy also enhances low-dose hydrocarbon-induced sarcogenesis.2 The transfer of the autoimmune hyperplastic disease from one animal to another, by the transfer of spleen cells, offers the opportunity to study the species of cells involved in the production or the inhibition of the various specific lesions. Such transfer can be accomplished using spleen cells from previously 3-day-thymectomized donors and a variety of suitable immunologically impaired recipients such as newborn mice, young adult nude mice, or young adult mice that had been thymectomized at birth (1, 2, 4). Thus, the model seems suitable not only for the study of autoimmune diseases, but for the investigation of the relationships between autoimmune reactions and oncogenesis.

Although the incidence of an autoimmune lesion might, in some cases, be reasonably high [i.e., about 30% of cases of gastritis in female BALB/cByJ mice that had been subjected to 3-day thymectomy (1)], it was not known whether the disease could be transferred with sufficient efficiency for practical purposes, especially if the donor spleen cells were obtained from animals that had not yet themselves developed overt autoimmune lesions. This paper reports that autoimmune gastritis was transferred from adult 3-day-thymectomized donors, prior to their development of overt disease, into young adults that had been thymectomized as newborns and that the incidence of disease in the recipients was remarkably high and greater than would have been the case among the donors themselves.

MATERIALS AND METHODS

BALB/cByJ mice were bred in our own specific-pathogen-free facility; births were recorded daily. When litters were 3 days of age, in the case of spleen-cell donors, or within the first 24 h of the lives of spleen-cell recipients, the animals were either thymectomized or sham thymectomized and then returned to their mothers.

The surgery was done under hypothermia. The pup was affixed to the operating board with carefully affixed rubber bands. A midline incision was made with iris scissors in the sternum across the distance of the first four ribs, and the wound was held open with curved forceps. Under a dissecting microscope, the lobes of the thymus were teased out with the aid of toothpicks, the ends of which had been split and covered with a thin layer of cotton. After removal of the thymus, air was gently squeezed from the thoracic cavity, and the wound was closed with one or two fine silk sutures; completeness of the thymectomy was eventually verified at autopsy. The sham procedure was identical except that the thymus was not actually removed, and the end of the tail was clipped for future identification. The operated pups were rewarmed under table lamps for several hours, the mother was induced to urinate on them (in order to prevent subsequent cannibalism), and they were then returned to their mothers' care until weaning at 4 wk of age. Survival was about 95%.

When the animals that had been subjected to surgery in the first day of life were 4 wk old, each mouse received from a single donor 10⁷ spleen cells i.p. The donors were approximately 3-mo-old syngeneic animals of the same sex, that had been either thymectomized or sham thymectomized at 3 days of age. The spleen cells were not pooled. As far as possible, each litter of recipient animals was distributed evenly among the various groups. At the time of spleen-cell transfer, autoimmune lesions were not grossly evident in either donors or recipients. When the recipients were 8 to 10 mo old, they were killed and examined for autoimmune disease.

This paper is confined to the occurrence of grossly apparent hyperplastic autoimmune gastritis. The stomachs were excised at autopsy, cut open along the lesser curvature, and placed in Tellysnickzcy's fixative. The lesions were judged by the thickness of the stomach wall and the size of the rugae and scored from 0 to 4. For the purpose of this study, only scores from 2 to 4 were considered positive. At the time of scoring, the observer was unaware of the group from which the stomach had been obtained.

RESULTS

Table 1 shows the overall incidences of overt gastritis among the various spleen-cell recipient groups. About half of the female and about 30% of the male recipients of the 3-day-thymectomized spleen cells had developed a grossly recognizable gastritis by 8 to 10 mo of age; this is considerably more than one would expect (P = 0.05, by χ² for the females; and P = 0.002, by Fisher's exact test for the males), since the incidence of gastritis, which was used for comparison, was, among 3-day-

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1 This work was supported by USPHS Grant CA 31837.
2 L. M. Prehn and A. Kojima, The paradoxical effect of three-day thymectomy on sarcogenesis with different dosages of methylcholanthrene, submitted for publication.
DISCUSSION

The high proportion of donors of both sexes that were capable of transmitting gastritis to the spleen-cell recipients was surprising, especially since the spleen cell donors had no overt disease at the time when their spleen cells were obtained for transfer. The expected incidence of gastritis among the donors, had they been allowed to live to develop disease, was only about 30% among the females and zero among the males (1). Nonetheless, 10 of 18 female donors and 6 of 15 male donors successfully transmitted the lesion. If only those donors that transmitted disease are considered, the incidence of gastritis among the recipients of those donors was 80% in the females and 64% in the males. These incidences are undoubtedly conservative, since they were based upon grossly evident disease. The expected incidence of gastritis among the donors was based upon microscopic analysis at 4 mo of age, and evidence was obtained to show that the incidence of autoimmune disease in this system does not rise significantly after about 4 mo (1).

Thus, the data seem to indicate that the transfer procedure may have preferentially favored those clones of spleen cells that were capable of causing autoimmune disease; perhaps the autoimmune effector cells were differentially stimulated, and/or the suppressor cells tended to be eliminated. Presumably, the same mechanism would be entrained when the donors had been merely sham thymectomized, but the starting proportions of these cells might be so different in that case that disease would rarely result; however, it did apparently occur in one case in the present study.

The fact that disease was transmitted in such high incidence, even from donors without gross disease, suggests that it may be feasible to use this system to investigate the cellular bases of the differences among various mouse strains in their overall susceptibilities to the induction of autoimmunity and neoplasia; also the cellular basis of the induction of various specific lesions, such as gastritis as opposed, for example, to oophoritis, may also be amenable to study.

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