EFFECT OF RECIPIENT'S AGE ON TRANSPLANTATION OF NEONATAL LYMPHOID ORGANS

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Recently, much attention has been paid to systemic mechanisms of changes in immunity arising during aging, the essence of which is the appearance of different kinds of signals, inhibiting the immune response, at a certain stage of ontogeny [1]. Meanwhile, age defects of the cellular microenvironment of autonomously developing lymphoid organs may also make a definite contribution to senile immunodeficiency [7, 10].

The aim of this investigation was to study the development of functions of transplanted lymphoid organs from newborn animals into young and old recipients, in order to assess to what degree the effectiveness of this development depends on the properties of the system in which it takes place. It was shown previously that cells of a transplanted organ die (except cells of the stromal microenvironment), and it is subsequently repopulated by precursor cells of the recipient's bone marrow [5]. Consequently, one-stage transplantation of thymus and spleen provides a model of maturation of precursor cells along the bone marrow – thymus – spleen axis, which is 'inserted' into animals at different ages. It has been shown in this way that age differences in the recipients' bone marrow from the point of view of the parameter chosen for study, are sufficiently small [6].

EXPERIMENTAL METHOD

CBA mice were obtained from the 'Stolbovaya' nursery, Academy of Medical Sciences of the USSR. Newborn animals of both sexes, namely 4-5-month-old females (young) and 21-22-month-old females (old) were used. Aging and reproduction of the mice took place in the animal house of the Institute of Gerontology, Academy of Medical Sciences of the USSR. Organs of the newborn animals (one lobe of the thymus and the spleen) were transplanted beneath the capsule of the left kidney of the young and old recipients, under callipsol anesthesia. In some cases the recipient's own spleen was removed during the operation. The relative number of direct antibody-forming cells (DAFC/10^6) in the spleen was determined 3 months after transplantation in the animals undergoing the operation in response to sheep's red blood cells (10^8) by the method of Jerne and Nordin [9]. The results were subjected to statistical analysis by parametric tests.

EXPERIMENTAL RESULTS

It will be clear from Fig. 1 that the presence of an additional donor's spleen did not affect the number of DAFC in the spleen of the young recipients compared with the age control. The low immune response in the donor's spleen compared with the recipient, will be noted. It can be tentatively suggested that, this was due not only to the heterotropic arrangement, but also to the competitive effect of the recipient's spleen, for its removal led to considerable growth both of the number of nucleated cells, namely from $(7.1 \pm 0.7) \cdot 5 \cdot 10^6$ to $(17 \pm 2.6) \cdot 5 \cdot 10^6$, and also the number of DAFC in the donor's spleen. Combined transplantation of the thymus and spleen into young recipients led to marked stimulation of the immune response in both the donor's and the recipient's spleen, and this effect was preserved after preliminary removal of the recipient's spleen. The picture was different after transplantation of the thymus and spleen of newborn animals into old recipients (Fig. 2). In this case there was

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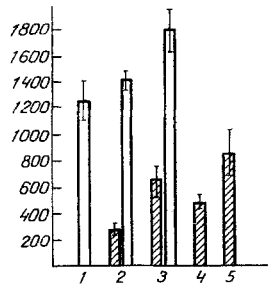

Fig. 1

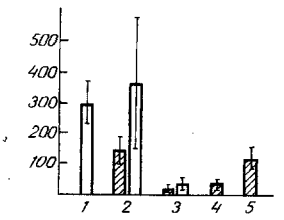

Fig. 2

Fig. 1. Relative number of DAFC (per 10^6 nucleated cells) in response to sheep's red blood cells in spleen of 8-month-old CBA mice after transplantation of lymphoid organs from newborn donors into them at the age of 5 months. Here and in Fig. 2: 1) intact animals, 2) intact animals with transplanted spleen, 3) intact animals with transplanted thymus (one lobe) and spleen, 4) splenectomized animals with transplanted spleen, 5) splenectomized animals with transplanted thymus and spleen. Ordinate, relative number of DAFC per 10^6 nucleated cells. Shaded columns indicate immune response in donor's spleen; at least 5-7 animals in each experimental group. Vertical lines on columns denote error of means.

Fig. 2. Relative number of DAFC (per 10^6 nucleated cells) in response to sheep's red blood cells in spleen of 25-month-old CBA mice after transplantation of lymphoid organs from newborn animals into them at age of 22 months.

marked inhibition of the immune response in both donor's and recipient's spleen — an effect which was not found after transplantation of the thymus alone [8]. However, preliminary removal of the recipient's spleen abolished this suppressor effect and, indeed, revealed a certain stimulating action of the transplanted thymus (Fig. 2: 3 and 5).

The results show that the ultimate effect of transplantation of the neonatal thymus and spleen into intact animals depends entirely on the recipient's age. In other words, functions of the 'inserted' autonomous system of immunity are determined by the age of the system into which it is 'inserted': stimulation of the immune response is observed in young animals, its inhibition in old animals. The nature of these depressive influences may differ: action of pituitary hormones [4], of suppressor factors of the thymus [2], spleen [3], and serum [11] of old animals, and so on. However, critical stages evidently exist in this complex inhibitory apparatus, and as the results described above show, one such stage is the spleen. In fact, the disturbance created in the old system of immunity by the transplanted thymus is transformed into immunosuppression in that system. Meanwhile, preliminary removal of the recipient's spleen virtually completely abolishes this suppressor effect, evidence that an autonomous program of development of transplanted lymphoid organs exists and can be realized, in the absence of inhibitory factors. Our results thus indicate that effective correlation of the immunity system during aging is possible only after preliminary destruction of the active mechanisms of inhibition that are formed.

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SEX DIFFERENCES IN NUMBER OF ESTROGEN RECEPTORS IN RAT LIVER CYTOSOL

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Many functions of the liver, which occupies a central place in metabolism and in the maintenance of homeostasis, exhibit sexual differentiation [4]. In particular, sexual dimorphism is observed in the activity of many of the enzymes of steroid metabolism, the content of corticosteroid-binding plasma globulin, and intracellular steroid-binding proteins (the unusual estrogen-binding protein UEBP) and androgen receptors in rats [2, 7, 10, 11, 15]. The latter, which determine differences in sensitivity of the liver in males and females to the action of androgens and estrogens, are themselves targets for regulatory and programming influences of the sex hormones.

As regards estrogen receptors (ER) of the liver, the question of the presence or absence of sex differences in their number and properties still remains unclear. Taking into account data on the role of ER in the realization of the direct effect of estrogens on projection of angiotensinogen, UEBP, and $\alpha_{2\mu}$-globulin by hepatocytes [3, 13, 15], the solution of this problem may be of fundamental importance for our understanding of the causes of the possible differences in their action on liver function in males and females. Data in the literature on this question are very contradictory [8, 9]. These contradictions are evidently connected with the inappropriateness of the methods used to determine ER by some workers in the rat liver. The point is that besides classical ER, UEBP with high binding capacity also are present in male rat liver cytosol [5]. The presence of UEBP adds significantly to the difficulty of precise quantitative determination of ER in the male rat liver.

The method which we suggested previously for determining ER in rat liver cytosol, with the use of sodium thiocyanate [1], has proved to be capable of the differential determination only of ER and not of UEBP. By using the method in [1] we demonstrated the existence of sex differences in the number of ER in the rat liver and we also studied the effect of gonads and the pituitary on this feature.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats. Males and females underwent gonadectomy at different stages of ontogeny. Animals undergoing mock operations at the same stages of ontogeny served as the control. Animals undergoing gonadectomy at different stages of ontogeny were used in the experiments on reaching the age of 12 weeks, whereas sexually mature animals were used 2-3 weeks after gonadectomy. Rats subjected to hypophysectomy were used in the experiments 3 weeks

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