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Estradiol Dependency of Tumor Growth, Levels of Steroid Receptor Contents and Enzymic Activities in Rat Breast Cancer Tissues†

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= Abstract = To study the nature of tumor growth and regression, the mammary cancer model in Sprague-Dawley rats, induced by N-nitrosomethylurea(NMU) was analyzed with a view of biochemical response to physiological modification of host estradiol system, such as ovariectomy, tamoxifen treatment or estradiol reinjection. The growth and regression of the tumors were monitored by the tumor size variation in response to the treatment. The surgical removal of estradiol generation system such as ovariectomy and the medical treatment of estradiol antagonist, tamoxifen, markedly decreased the tumor size within two weeks, while the replenishment of estradiol by intraperitoneal reinjection stimulated the tumor growth. With these changes of tumor size, the efficiency of the functional hormonal apparatus was checked by determination of the contents of the estradiol and progesterone receptor in the cytosol and nuclear fractions, respectively. The receptor analysis showed that the contents of the cytoplasmic estradiol and progesterone receptor varied directly in response to estradiol state of the host; namely, decreased level at reduced tumor volume and increased level at tumor-stimulated state. The changing patterns of the contents of the nuclear estradiol and progesterone receptors were similar to those of the cytoplasmic ones. In relation with the changes of receptor contents, the radical-related enzymes were monitored for their activities such as peroxidase, catalase, superoxide dismutase and glutathione transferase. Among them only the peroxidase activities showed the positive correlation with the estradiol receptor contents. These results indicated that the growth and regression of the mammary tumors could be deeply related with the receptor status of estradiol system and the activities of peroxidase.

Key Words : ***Estradiol dependency, Tumor growth, Steroid receptor, Rat breast cancer***

INTRODUCTION

There are two alternative strategies to solve the tragic problem of human cancers; namely, prevention of carcinogenesis and treatment of established cancers. Both of the strategies could be solved only through the elucidation of carcinogenesis mechanism and cancer growth nature (Aaronson & Tronick 1985). However, the mystery of carcinogenesis and cancer nature are still far from being unveiled. The most essential point of these failure in cancer eradication stands from the lack of knowlege on the nature of tumor growth as well as the exact mechanism of carcinogenesis. In this regard, it is very urgent to identify and study the physiological condition which might affect the tumor growth or

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regression. For this purpose, the chemically induced breast cancer model in the rats is one of the best system from several aspects, such as easy induction, short latent period, reproducibility of tumor, discrete stage effect of physiological state on carcinogenesis and tumor growth, definite endocrinologic dependence, being analogous to human cancer, and easy to handle and monitor (Gullino *et al.* 1975; Moon *et al.* 1976; Arafah *et al.* 1982). Since breast cancers, not only of rats but also of human, showed the estradiol dependency for growth, the counterstrategies to minimize the production and utilization of estradiol could have been the choice of therapy, such as ovariectomy and E_2-antagonist (tamoxifen) treatment (Skinner *et al.* 1980; Kim *et al.* 1982a). And the prognosis of these tumors could be readily determined by the diagnostic determination of steroid receptor contents in the breast cancer samples; that is, the higher the receptors were, the better the prognosis of the cancers would be (Horwitz *et al.* 1975; Brooks *et al.* 1980). In the present experiment, we have assumed that if the tumor growth and regression were dependent on estradiol state, the receptor content of the tissues should be fluctuated in response and some of the radical generation or scavenging system could be the early signals in relation, because the radicals may explain the tissue damage phenomenon in the state of tumor regression. To test our assumption, we induced the breast cancers on Sprague-Dawley female rats by N-methylnitrosourea injection and the tumor bearing rats were divided into 4 different groups; namely, control, ovariectomized, ovariectomy plus estradiol injection, and tamoxifen groups. On these tumors, we have monitored the sequential changes of the contents of cytoplasmic estradiol and progesterone receptors, nuclear estradiol and progesterone receptors and enzymic activities of catalase, peroxidase, superoxide dismutase, and glutathione transferase in the tissues.

MATERIALS AND METHODS

1. Reagents

Chemicals were purchased from the following sources; N-nitrosomethylurea(NMU), estradiol, diethylstilbestrol, PPO, POPOP, O-dianisidine and dithiothreitol from Sigma Chemical Co. (St. Louis. Mo. USA), (2.3.6.7.H^3) estradiol (110 Ci/mmol), (17alpha-methyl H^3) promegestone (87 Ci/mmol), and R5020 from New England Nuclear Co. (Boston, Mass, USA), Dextran T-70 from Pharmacia Fine Chemicals AB Co. (Uppsala, Sweden), Norit A charcoal from Fisher Scientific Co. (FairLawn, N.J. USA). And other chemicals of analytical grade were purchased from the commercial sources.

2. Breast cancer induction and groupings

Breast cancers were induced by the single intravenous administration of NMU (5 mg/100g weight) at the age of 50 days on Sprague-Dawley female rats after Gullino *et al.* (1975). Approximately after 4 months of carcinogen treatment, the tumor bearing rats were identified and grouped into 4 different parts; such as the control group, oophorectomy group, oophorectomy+estradiol group and tamoxifen group. The bilateral oophorectomy was performed through the abdominal midline incision under light pentothal anesthesia and the injection of estradiol (5 μg per head), or tamoxifen (50 μg per head) was conducted intraperitoneally and daily for the study period.

3. Sample collection and storage

The experimental tumors were excised and divided into two parts; one part was fixed in formalin solution for histologic analysis and the other part was rapidly frozen with liquid N_2 and stored at deep freezer (Revco, SEH 653) under -80°C until the assay of receptor contents and enzymic activities.

4. Monitoring of tumor size

The variation of tumor size in response to the treatment was monitored twice a week with calipers for their long and short diameter determination.

5. Determination of steroid receptor contents

For the receptor analysis, approximately one gram of tumor specimens, confirmed histopathologically to be mammary adenocarcinomas, was minced down and homogenized in five volumes of TED buffer (Tris 10 mM, EDTA 1.5 mM, dithiothreitol 0.5 mM, glycerol 10% pH 7.4) with polytron homogenizer (Biotron, Swiss). The homogenate was centrifuged at 10,000×g, 4°C for 30 minutes (High-speed Refrigerated Centrifuge, MSE), and the supernatant fraction was collected for the subsequent receptor analysis and enzymic assay. Determination of cytoplasmic and nuclear estradiol and progesterone receptor contents in the tumor specimens were essentially after dextran-coated charcoal methods of McGuire (1973) with some modification as described previously (Kim *et al.* 1982a, b & 1983).

6. Determination of enzymic activities

The enzymic activities of the tumor tissues were determined after the standard procedures, respectively, such as peroxidase with O-dianisidine (Kim *et al.* 1984), superoxide dismutase after Marklund (1976), glutathione transferase after Habig (1974) and catalase after Feinstein (1964).

RESULTS

1. Modification of tumor growth by estradiol blocking system

The variation of the tumor size was monitored periodically after estradiol blocking treatment such as oophorectomy or tamoxifen treatment as Fig. 1. The tumor size of the control group increased continuously, while that of ovariectomized group decreased. The tamoxifen treated group also showed the same pattern as the overiectomized group. And the ovariectomized group regained the tumor growing power after the estradiol treatment. These results illustrated the definite dependence on the estradiol state for the tumor growth and regression.

2. Variation of steroid receptor contents in response to estradiol state

The contents of the steroid receptor such as cytoplasmic estradiol and progesterone receptor in the rat breast cancers showed the dependence on the estradiol state of the host. As shown in Fig. 2, the average cytoplasmic estradiol receptor content in the rat breast cancer tissues was about 250 fm/mg protein but after the ovariectomy or tamoxifen treatment, it decreased down to the level of 50 fm/mg protein. However, with the reinjection of estradiol, it increased up to 400 fm/mg protein. In case of cytoplasmic progesterone receptor, the situation was similar, that is, approximately 180 fm/mg protein at control, decreased to 20 fm/mg protein after ovariectomy or tamoxifen treatment and increased to 250 fm/mg protein by estradiol reinjection. However in cases of nuclear steroid receptor contents, such a fluctuation in the content was not prominent. As shown in Fig. 2, the nuclear estradiol and progesterone receptor contents showed only the marginal variation in response to estradiol blocking or addition.

3. Changes of enzymic activities in response to the estradiol state

In the present experiment, we have monitored the enzymic activity changes in the breast cancer tissues in response to the estradiol effect. In particular, we were interested in the enzymes related with radical generation and scavenging, such as peroxidase, superoxide dismutase, glutathione transferase and catalase. With the analysis of these enzymic activities in the cancer tissues, we could observe the prominent fluctuation pattern only of the peroxidase in response to the estradiol state of the host. Enzymic activities, other than peroxidase, did not reveal any significant fluctuation in re-

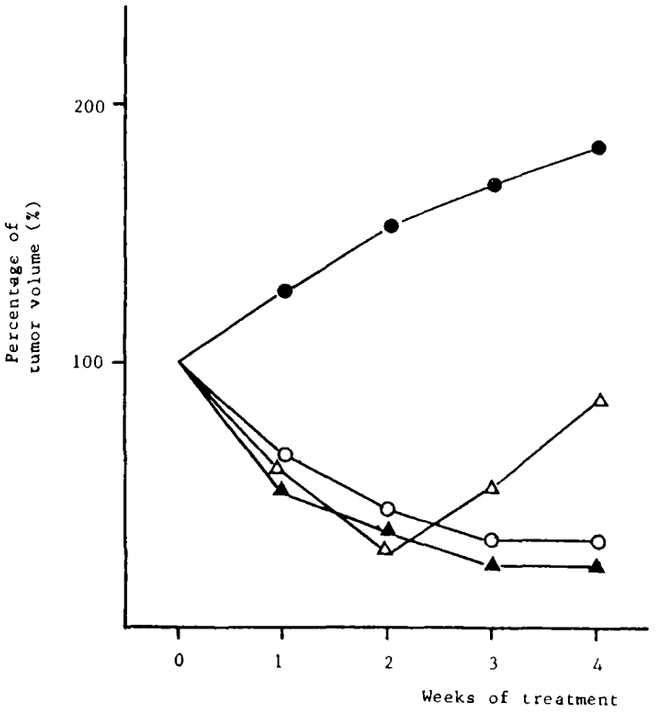

Fig. 1. Change of tumor size in response to hormone therapy to NMU-induced mammary carcinomas (●control, ○tamoxifen treatment, ▲ovariectomy, △ovariectomy+estradiol injection).

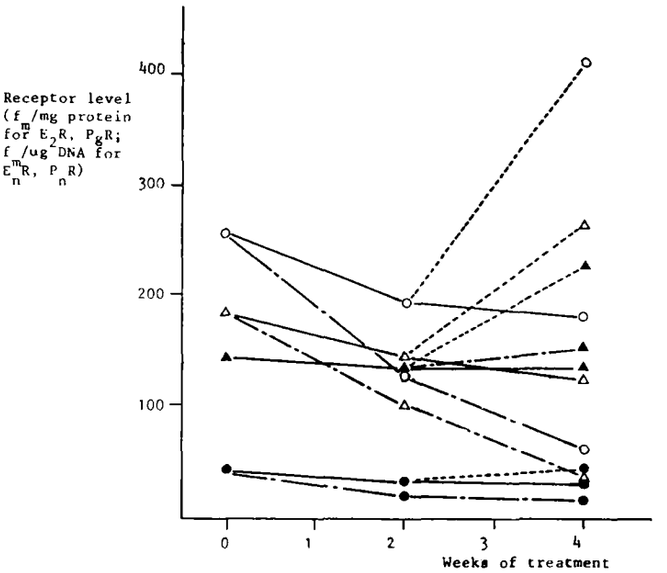

Fig. 2. Changes of E_2R, E_nR, P_gR, P_nR levels in the NMU-induced breast cancers (○E_2R, ●E_nR, △P_gR, ▲P_nR, ——after oophorectomy, — · —after tamoxifen treatment, ----E_2 injection after oophorectomy).

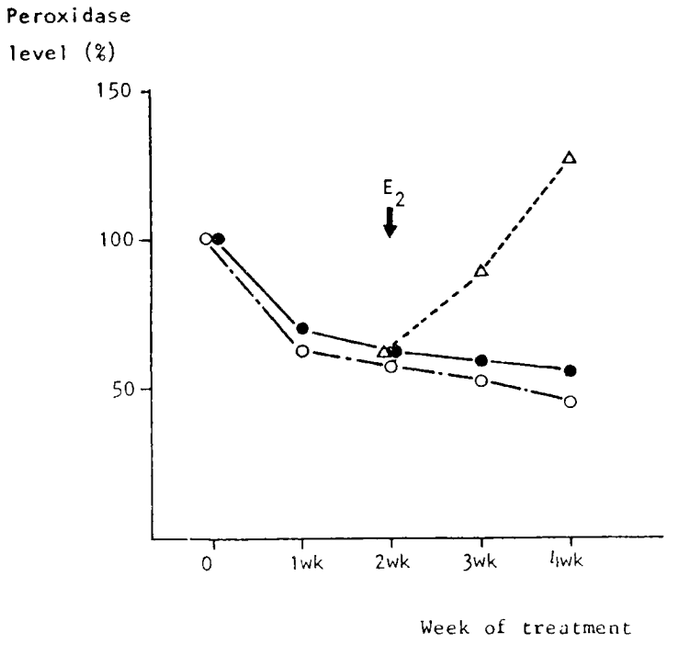

Fig. 3. Estradiol effect on the levels of peroxidase in the NMU-induced breast cancers (●oophorectomized group, △E_2 injection two weeks after oophorectomy group, ○tamoxifen treated group).

sponse to estradiol state (data not shown). The enzymic activity of the peroxidase showed the parallel change to those of cytoplasmic estradiol and progesterone receptors in response to ovariectomy, tamoxifen treatment and estradiol reinjection as shown in Fig. 3. After estradiol blocking, the specific peroxidase activity in the breast cancer tissues decreased to 50% of the control level, while by estradiol reinjection, it increased to 120% of the original state. These results illustrated the parallel changes of the steroid receptor contents and peroxidase enzymic activities, which suggested the common signal transducing system among them for tumor growth and regression.

DISCUSSION

The majority of mammary carcinomas induced by DMBA or NMU regress rapidly after ovariectomy or tamoxifen treatment (Vignon & Rochefort 1976; Arafah *et al.* 1980 & 1982). This estradiol dependency of the mammary tumors for growth was elucidated not only *in vivo* tumors but also *in vitro* cell or organ culture systems (Shafie & Brooks 1977; Koh 1983; Malarkey *et al* 1983; Yang & Kim 1983; Arafah *et al.* 1984a & b, Kimm *et al.* 1984, Simon *et al* 1984). This changing mode of tumor growth was reproduced in the present experiment by surgical and medical treatment to the NMU induced mammary cancers (Fig. 1). Ovariectomy and tamoxifen treatment induced the tumor regression to the 5 percentage of original size after two weeks, but after the estradiol reinjection, tumors regained the growing power and had grown rapidly, which suggested the estradiol dependency of the tumor growth. The hormone dependency of these tumors should be explained in terms of hormone action mechanism. The steroid hormones, including estradiol, have the similar action mechanism. The target cell has the specific, high affinity receptors, which bind the attacking hormones. After binding, the hormone-receptor complexes are transformed and later translocated to the nuclear sites, where the specific set of genes are activated to produce the certain functional proteins, which are responsible for actual hormone action (Jensen *et al.* 1968; Jensen & DeSombre 1973). Actually, from the action mechanism, it was deduced that the higher the receptor content in the tumor tissue were, the more sensitive the tumor would be to the hormone therapy. Therefore in the management of breast cancer, the cytoplasmic estradiol and progesterone receptor contents were being used as the best indices to decide the therapeutic direction and prognosis. In other words, if high receptor content, the blocking of receptors by antagonists or elimination of estradiol source by surgical removal could be the choice of therapy leading to interruption of growth and induction of regression of tumors.

In our previous experiment, we found that the consequent regressed state of the mammary tumor by ovariectomy or tamoxifen treatment, had very low level of cytoplasmic receptors for estradiol and progesterone (Koh 1983; Yang & Kim 1983; Kimm *et al.* 1984). But it is not clear why the regressed tumor state has the low level of receptors, whether through decrease of estradiol dependent biosynthesis, or degradation of the receptors. Therefore we tried to pursue the phenomenon of steroid receptor content variation in response to estradiol state of the host by checking each step of the estradiol action mechanism; namely, cytoplasmic ER, nuclear ER and the E_2 dependent products, serially before and after ovariectomy, tamoxifen treatment and estradiol reinjection. As shown in Fig. 2, ovariectomy and tamoxifen treatment caused a drastic reduction in the content of both ER and PgR, which was relieved by E_2 reinjection. Although not prominent, the nuclear receptor content showed the similar changing pattern as cytoplasmic recep-

tors. For the variation of estradiol receptor contents, there are controversial reports. The biosynthesis of ER is necessary for maintenance of ER activity (Jakes *et al.* 1984), which is stimulated by estradiol (Gorki *et al.* 1971, Jensen *et al.* 1971), prolactin (Vignon & Rochefort 1976; Shafie & Brooks 1977, Malarkey *et al.* 1983; Arafah *et al.* 1984b; Simon *et al.* 1984) and cyclic nucleotides (Cho-Chung 1974; Cho-Chung & Caullino 1974) or modified by the growth (Brooks *et al.* 1984; Murphy *et al.* 1984). And the functional efficiency of ER might be regulated by the endogenous inhibitor, which is rich in normal cytosol and poor in tumor cytosol (Markaverich 1984), by the covalent modification of the receptor through phosphorylation-dephosphorylation system (Auricchio *et al.* 1984; Puri *et al.* 1984), or by the stability control through protein degradation mechanism such as plasminogen activator (Sherman *et al.* 1980; Yamashita *et al.* 1984). Therfore it is very difficult to conclude in simple terms to explain the changes of the ER binding character in response to estradiol state of the host. As for the estradiol dependent functional proteins, a few proteins are reported such as progesterone receptor (Horwtz *et al.* 1975), lactate dehydrogenase (Burke *et al.* 1978), tissue plasminogen activator (Yamashita *et al.* 1984), peroxidase (DeSombre *et al* 1975; Keenan *et al.* 1979; Kimm *et al.* 1984), 28K protein (McGuire *et al.* 1984) and 46K protein (Westley & Rochefort 1979). To explain the estradiol dependency of the tumor, we must pay our attention to these hormone dependent proteins. LDH is related with the anaerobic glycolysis, while plasminogen activator plays the role in tumor invasion and metastasis (Carlsen *et al.* 1984). And PgR mediates the variety of progesterone action in relation with other complex endocrinologic signals (Horwitiz *et al.* 1975). But the variation of peroxidase level attracted our attention on the assumption that the regression and growth stimulation of the tumor might be effected through radical generation and scavenging system. Thereby, we examined the quantitative change of enzymes, related in radical turnover such as catalase, glutathione-S-transferase, superoxide dismutase as well as peroxidase in the tissues. Among those enzymes, we could observe the changes only in the peroxidase activities. Therefore we could not make our conclusion whether radicals might play the dominant role in tumor growth and regression in the present study. It might be necessary to monitor directly the quantitative changes of radicals and other degradation enzyme systems further to reveal the tumor growth nature (Troll *et al.* 1982). Anyway, it attracts our attention that, the peroxidase activity might be related with the estradiol turnover via oxidation of estradiol and with the bactericidal or virucidal activity in association with halides and H_2O_2 (Belding *et al.* 1970).

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= 국문초록 =

흰쥐 유암의 estradiol 의존성 암성장에 따른 steroid 수용체 함량과 효소활성의 변화

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암의 성장과 퇴화에 따르는 성상을 구명하기 위한 노력의 일환으로, Sprague-Dawley순계 암컷 쥐에게 N-nitrosomethylurea(NMU)의 미정맥주입에 의해 유도한 유암을 실험모델로 하여, 숙주의 estradiol호르몬계에 난소적출술, tamoxifen처치, 또는 estradiol의 투여 등으로 생리적인 변화를 일으킨 뒤 야기되는 생화학적 반응을 구명하고자 하였다. 암의 성장과 퇴화는 처치의 경과에 따른 암의 크기 변화로 검정하였는 바, 난소적출술 또는 항estradiol 제제인 tamoxifen의 투여는 처치후 2주내에 암의 크기를 현저하게 감소시켰으며, 이들 암종은 다시 estradiol의 복강내 투여로 성장이 크게 촉진되었다. 이러한 암의 크기 변화와 더불어 estradiol hormone의 기능적 효율의 변화를 이들 암종의 세포질성 및 핵성 estradiol과 progesterone 수용체를 각각 측정하여 비교하여 본 결과, 세포질성 estradiol 및 progesterone 수용체의 함량은 숙주의 estradiol state와 정비례적인 변화를 보이는 바, 즉 암의 크기가 작아지는 경우 수용체 농도가 낮아지고, 커지는 경우 수용체 농도가 높아져 갔다. 한편 핵성 수용체의 농도변화는 현저하지 못하지만, 세포질성 수용체의 농도 변화와 유사한 경향을 보였다. 이러한 steroid수용체의 농도변화와 더불어 radical의 생성, 이용, 처리에 관여하는 효소들 즉 peroxidase, catalase, superoxide dismutase 및 glutathione transferase 등의 활성변화를 측정 비교하여 본 결과, 이중 peroxidase만이 estradiol수용체 농도변화와 정비례적인 활성변화를 가지고 있음을 알 수 있었다. 이러한 결과로서 유암의 성장과 퇴화는 estradiol 호르몬계의 작동기구 및 peroxidase가 중요한 역할을 하고 있음을 밝힐 수 있었다.