Mammary Tumors in HER-2/NEU Mice Are Characterized by Low Content of Estrogen Receptors-α and Absence of Progesterone Receptors

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Transgenic mice carrying erbB2(HER-2)neu gene are characterized by high incidence of mammary adenocarcinoma. The content of estrogen receptor was no more than 10 fmol/mg protein in 8 of 14 studied tumors, while the content of progesterone receptors was even lower in all 14 studied tumors. Based on these data, we distinguish two subtypes of HER-2/neu-adenocarcinomas in mice: ER^+,PR^- and ER^-,PR^-, which can be used for the development of new approaches to the treatment of receptor-negative mammary gland tumors.

Key Words: *HER-2/neu gene; transgenic mice; breast cancer; steroid receptors*

HER-2/neu protein (c-erbB2) belonging to the family of erbB2 receptors and receptor tyrosine kinases has no special ligand, but is an important component in the transduction of the proliferative signal from peptides similar to the epidermal growth factor [4]. Transgenic mice carrying erbB2(HER-2)/neu gene are characterized by short life span and high incidence of mammary adenocarcinoma [1,4]. Estradiol suppressed the expression of c-erbB2 in breast cancer cells containing estrogen receptors (ER), but not in transformed cells lacking ER [6]. There is an inverse correlation between the incidence of HER-2/neu expression in human mammary tumors and the presence of sex steroid hormone receptors [8]. High expression of HER-2/neu is regarded as a possible cause of resistance to hormone therapy [7]. We evaluated the content of estrogen and progesterone receptors in mammary tumors of female mice carrying erbB2(HER-2)/neu oncogene and thus additionally characterized the hormone dependence of these tumors.

MATERIALS AND METHODS

Female FVB/N mice carrying HER-2/neu gene were used in the study. The animals were received from Italian National Research Center of Aging and bred at Laboratory of Carcinogenesis and Aging, N. N. Petrov Institute of Oncology. When mice reached the age of 6.5-7 months, 14 animals with clearly palpated tumors were sacrificed with ether, the tumors were resected, the adjacent tissues were removed, and the tumors were kept in liquid nitrogen till evaluation of ER and progesterone (PR) receptors. ER and PR were measured by competitive radioligand assay [12] using labeled ET and PR (Amersham). The results were expressed in fmol/mg protein. Protein content was measured by Lowry's method. The results were processed by the standard statistical method.

RESULTS

All collected tumors were adenocarcinomas by histological structure. They virtually did not differ by weight and time of material collection, which confirms phenotypical homogeneity of the group. However, the material was divided into two groups: tumors containing ER but not PR and tumors containing neither ER nor PR (Fig. 1).

These data suggest that adenocarcinomas in HER-2/neu transgenic mice are characterized by relative dependence on ER, because they contain no typical estrogen-inducible protein (PR receptor). It is however

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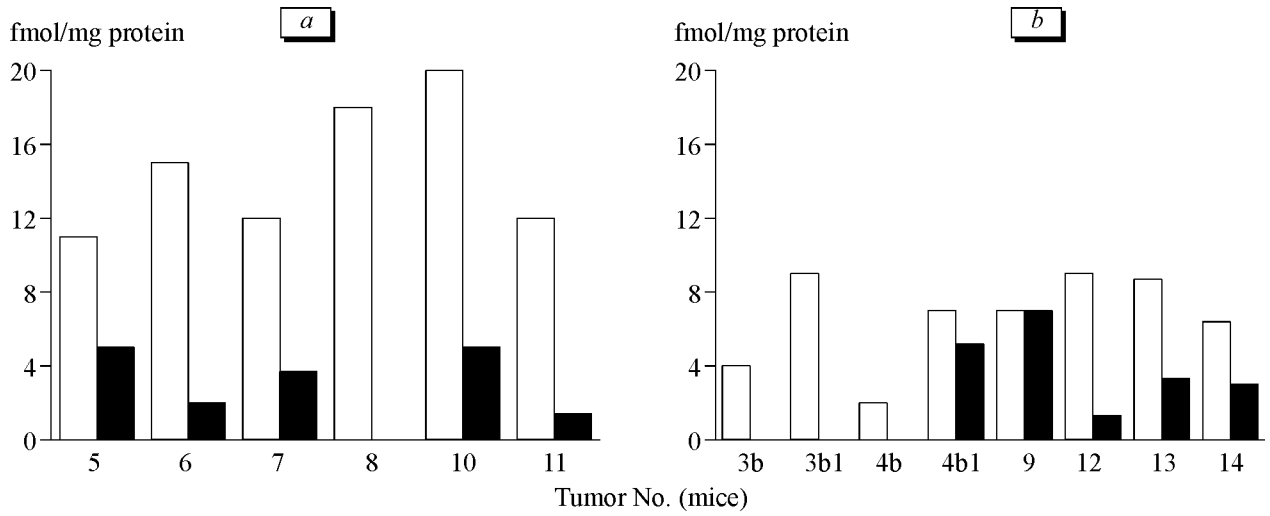

Fig. 1. Subgroups ER^+,PR^- (*a*) and ER^-,PR^- (*b*) of mammary tumors in HER-2/neu female mice. Light bars: ER tumors; dark bars: PR tumors.

possible that even low concentrations of ER in these tumors are sufficient for inhibition of their growth after overiectomy performed at the age of 2-2.5 months. According to indirect data based on evaluation of the effects of repeated pregnancies, lactation, and tamoxiphene and similar peculiarities of transplanted neu^+ tumor growth in males and females, mammary tumors in transgenic HER-2/neu mice can be classified as hormone-independent or partially hormone-dependent [9]. The latter fact is confirmed by our own data and by the fact that similar picture was observed in human breast tumors. For example, in women a combination of HER-2/neu^+ with steroid hormone receptors in breast cancer tissue is much more rare than HER-2/neu carriership in the absence of steroid receptors and, which is particularly important, this latter combination is characterized by highly aggressive tumor growth [2,8].

The competitive radioligand assay for evaluation of steroid receptors allows measurement of mainly one type of ER in tested tissue, estrogen receptor-α [5]. Only additional studies can show whether estrogen receptor-β [11] is present in adenocarcinoma tissue of HER-2/neu transgenic mice. However, our findings and the significance of search for additional means of treatment and prevention of receptor-negative breast cancer (tyrosine kinase and cycloxygenase-2 inhibitors, retinoids, IFN and their inductors, and many other compounds belong to these means [3,10,13]), we conclude that the model used in our study deserves attention.

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REFERENCES

1. V. N. Anisimov and I. N. Alimova, *Uspekhi Gerontol.*, No. 7, 72-94 (2001).
2. L. M. Bershtein, *Hormonal Carcinogenesis* [in Russian], St. Petersburg (2000).
3. E. V. Tsyrlina, E. V. Bakhidze, A. T. Volkova, *et al.*, *Vopr. Onkol.*, **47**, 214-217 (2001).
4. E. R. Andrechek and W. J. Muller, *Breast Cancer Res.*, **2**, No. 3, 211-216 (2000).
5. J. P. Brouillet, M. A. Dujardin, D. Chalbos, *et al.*, *Int. J. Cancer*, **95**, 205-208 (2001).
6. M. De Bortoli, C. Dati, S. Antoniotti, *et al.*, *J. Steroid Mol. Biol.*, **43**, 21-25 (1992).
7. M. Dowsett, *Endocr. Related Cancer*, **8**, 191-195 (2001).
8. M. Ferrero-Pous, K. Hacene, C. Bouchet, *et al.*, *Clin. Cancer Res.*, **6**, 4745-4754 (2000).
9. S. Menard, P. Aiello, E. Tagliabue, *et al.*, *Cancer Res.*, **60**, 273-275 (2000).
10. R. I. Nicolson, I. R. Hutcheson, M. E. Harper, *et al.*, *Endocr. Related Cancer.*, **8**, 175-182 (2001).
11. G. Palmieri, G. J. Cheng, S. Saji, *et al.*, *Ibid.*, **9**, 1-13 (2002).
12. M. Saez, P. Martin, and C. D. Chouvet, *Cancer Res.*, **38**, 3468-3473 (1978).
13. K. Wu, Y. Zhang, X. C. Xu, *et al.*, *Ibid.*, **62**, 6376-6380 (2002).