Histological Studies of the Mode of Origin of Tumors

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UsuBUCHI, I., KuDO, H. and SATO, T. Histological Studies of the Mode of Origin of Tumors. Tohoku J. exp. Med., 1981, 133 (3), 325-330 — All of the tubular adenocarcinomas of early gastric cancer in humans showed gentle transitions from surrounding normal to neoplastic epithelium. In mammary carcinomas in C3H/He mice, known as viral tumors, there were also transitional appearances from normal to cancer cells. Furthermore, it was possible in rats to trace gradations between normal fibrocytes and sarcoma cells in marginal areas of tumors induced subcutaneously by 3-methylcholanthrene (MCA). It cannot be explained by the mutation of a few somatic cells that transitions from normal to neoplastic cells were observed not only in viral tumors in mice but also in human carcinomas and in chemically induced tumors in rats. It seems well to think of the mode of origin of all types of tumors as an excessive cellular regeneration to make up for the functional disturbance of cells invaded by oncogenic viruses. ——— mode of origin of tumors; histological transitions; excessive regeneration; oncogenic viruses

There is no agreed opinion on carcinogenesis. The most prevalent theory has been that of the somatic mutation (Bauer 1963). However, the viral theory (Rous 1936; Gye 1938; Gross 1970; Todaro and Huebner 1972) and the epigenetic theory (Monod and Jacob 1961; Sugimura et al. 1966) are also insisted on. The advocates of these theories generally intend to interpret the origin of all types of tumors by their own theory. On the other hand, some investigators think that there are some modes of origin of tumors available. So, now, the concept of carcinogenesis is remarkably in confusion.

In these circumstances, comparative histological observations on human gastric cancers, virally and chemically induced tumors in animals were carried out. As a result, transitions from normal to neoplastic cells in marginal areas of those tumors were commonly confirmed. On the basis of these findings, our concept of the mode of origin of tumors is advocated.

MATERIALS AND METHODS

Early gastric cancers

A series of 30 consecutive cases, diagnosed by us as tubular adenocarcinomas of early gastric cancer according to "the general rules for the gastric cancer study in surgery and pathology" by Japanese Research Society for Gastric Cancer (1974), were employed.

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Mammary carcinomas in C3H/He mice

Ten spontaneous mammary carcinomas in C3H/He mice, about 15 mm in diameter, were used.

MCA-induced sarcomas in rats

Pellets of paraffin containing 5 percent MCA were subcutaneously inserted in adult non-inbred rats of both sexes of Gifu strain. Ten nodules grown to about 5 mm in diameter, which were histologically confirmed to be neoplastic, were used. Furthermore, 20 MCA-induced sarcomas, about 20 mm in diameter, were also observed.

Sectioning and staining

The resected specimens of the stomach were routinely fixed in 10 percent formalin, and semiserial sections were made in obedience to the rules described above. In smaller MCA-induced sarcomas, serial sections of 5 μm were prepared. Mammary carcinomas and larger MCA-induced sarcomas were cut at the midline of the nodule and the cut surface was prepared. The sections were histologically examined by staining with hematoxylin and eosin. Reticulin impregnation, PAS and alcian blue staining were also utilized.

RESULTS

At areas in contact with normal mucous epithelium, all of 30 cases of tubular adenocarcinoma of early gastric cancer in humans exhibited transitions from normal to neoplastic epithelial cells, although the frequency and degree varied. In 18 of 30 cases, plain transitions between both tissues were detected. It was impossible to point out the clear-cut border line. In some cases, gradations between normal and neoplastic cells were observed in one and only tubulus (Figs. 1, 2).

In mammary carcinomas in C3H/He mice, plain transitions were shown in all cases in boundary areas between normal and neoplastic tissue (Fig. 3).

In all cases of smaller MCA-induced nodules, there were seen localized

Fig. 1. Human early gastric carcinoma, showing transitions from hyperplastic to neoplastic gland in the marginal area of the tumor. H.E., × 175.
clusters composed of atypical fibrocytes in the fibrous tissue. It was possible to recognize transitions from intact to those atypical fibrocytes (Fig. 4). Transitions from normal to neoplastic fibrocytes were observed in all cases of larger MCA-induced sarcomas in marginal areas (Figs. 5, 6). It was especially remarkable that gradations between normal and neoplastic fibrocytes were seen in areas distant from MCA inserted.

DISCUSSION

It was pointed out by Willis (1967) that transitions from normal to neoplastic
tissues were traced in marginal areas of early carcinomas. The present examination of early gastric cancers in humans exhibited the same transitional findings as Willis described. The careful microscopic examination of carcinomas of other parts, such as the colon, mammary gland and uterine cervix, did also afford the clear evidence of similar transitional changes. Moreover, it was also seen that gradations between normal and neoplastic tissues were traced, as in human carcinomas, in the experimental animal tumors such as viral mammary carcinomas in mice and chemically induced tumors in rats. Gross (1970) observed plain

Fig. 4. Early neoplastic change of the rat, showing transitions from hyperplastic to atypical fibrocytes in the fibrous tissue surrounding MCA-pellet. H.E., × 175.

Fig. 5. MCA-induced fibrosarcoma of the rat, showing transitions from normal to neoplastic fibrocytes in the marginal area of the tumor. H.E., × 175.
transitions between normal and neoplastic tissues in multicentric parotid tumors in C3H/He mice to which C58 leukemic filtrat was injected at the newborn period. Sasaki and Yoshida (1935) described that, in carcinogenesis of liver cells by using o-amidoazotoluol, multiple adenomas showing transitions from normal liver cells were induced at first and then more anaplastic cell cluster, namely liver cell carcinoma, arose in those adenomas and that the direct change from normal to carcinoma cells was not observed.

It is impossible to understand that all transitions from normal to neoplastic tissue in marginal areas of tumors are due to the somatic mutation of a few cells. It is also very difficult to relate these transitions with the gene change of cells by viruses, because it is analogous to the somatic mutation by viruses. By way of explanation for transitions from normal to neoplastic tissues, the theory of "field of origin" of tumors, which assumes a neoplastic change in vast numbers of cells over more or less extensive fields of tissue to which effective carcinogenic stimuli have been applied at some time in the past, was advanced by Willis (1967). However, this concept cannot explain the transitional change in marginal areas distant from inserted MCA in considerably larger MCA-induced sarcomas like our present ones.

In view of these facts, we wish to advocate that the tumor is not a mutational growth but an excessive regenerative growth in order to compensate for the important function of cells damaged by oncogenic viruses. The cells which exhibited not so excessive regeneration, giving mild atypia, on account of weak damages by invasion of viruses correspond to benign tumors. On the contrary, malignant tumors accord with cells of markedly excessive regeneration to make up for intense damages, showing severe pleomorphism or variation in size and shape. The invasion and metastasis, both being considered as the expression of autonomy
of malignant tumors, seem to be due to the dissociation from the proper continuation of cells as a result of the excessive regeneration. The autonomous proliferation due to the dissociation from the proper continuation is routinely observed not only in tumor cells but also in endometriosis, where cells of normal endometrium dissociated from the proper continuation are implanted in distant places. Both the abnormal proliferation of normal human cells xeno-transplanted into cortisonized or irradiated rats (Toolan 1957) and the induction of liver cell carcinoma by transplantation of normal liver cells into syngeneic mice (Leduc and Wilson 1963) may be also interpreted as the proliferation due to the dissociation from the proper continuation of cells.

As the foregoing account shows, our concept may be easily acceptable in viral tumors; however, what is the case of chemically induced or irradiation-induced tumors? MCA-induced sarcomas in our experiments, which are representative of chemically induced tumors, showed transitions from normal to neoplastic cells similar to those in viral tumors. As Gye (1938), Gross (1970) and Todaro and Huebner (1972) pointed out, dormant viruses activated by chemical agents or by irradiation may be able to invade intact cells, and the mechanism similar to that in viral tumors may be evoked in chemically induced or irradiation-induced tumors. Thus, the mode of origin of all types of tumors seems to be explained consistently by our concept.

References