Preferential Sites of Growth of Human Tumors in Nude Mice following Subcutaneous Transplantation

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ABSTRACT

The growth characteristics and biological behavior of human tumors transplanted s.c. into two different anatomical regions of nude mice were studied. It was observed that tumors transplanted in the anterior lateral thoracic wall grew faster than did tumors transplanted in the posterior aspect of the trunk. Anteriorly growing tumors, in contrast to the posteriorly transplanted ones, were better vascularized, showed less necrosis, invaded the tumor bed, and metastasized to the regional lymph nodes. These findings were independent of their histogenetic and morphological characteristics. It is concluded that regional vascular supply is a key factor influencing the biological behavior of the transplanted tumors and that it may affect tumor response to treatment as well.

INTRODUCTION

The lack of a functional thymus-dependent immune system in nude mice has made possible the transplantation of many human tumors into these animals (5-7, 19). Many reports have indicated that transplanted human tumors preserve the biological and biochemical characteristics of the tumor of origin (5, 12, 13, 16, 18). Furthermore, several studies have shown a correlation between human tumor xenograft response to chemotherapy and clinical results with the same drugs in cancer patients (4, 8-11, 14, 15, 17). These observations have stressed the potential value of the nude mouse system in testing the sensitivity of transplantable human tumors to various treatments (chemotherapy, radiation, etc.).

Published reports have indicated that tumors originating in various strains of conventional mice showed marked regional growth differences when transplanted i.d. into their syngeneic host (2, 3). In view of this information and the ever increasing interest in the nude mouse as a carrier of human tumors, we decided to investigate whether the same applies to the nude mouse-human tumor xenograft system in which human tumors are transplanted and grow mainly s.c. We also paid attention to the question of whether existing regional growth differences were related to histogenetic and morphological tumor characteristics as well as to the influence the site of transplantation may have upon the biological behavior of the transplanted tumors. The present paper attempts to answer these questions.

MATERIALS AND METHODS

For the purpose of the present study, 4- to 6-week-old female nude mice (nu/nu) were purchased from Sprague-Dawley, Madison, Wis. All mice were maintained in a pathogen-free environment. Human epithelial tumor cell lines grown in tissue culture and human tumors removed at surgery and directly transplanted into nude mice were used. All tested tumors were established in nude mice before the initiation of the experiment. The following tumor cell lines were used: Capan-1, a pancreatic carcinoma, and RT-4, a transitional cell carcinoma of the bladder, were provided by Dr. J. Fogh of the Sloan-Kettering Institute for Cancer Research, Rye, N. Y. Lines SW-780 and SW-800, derived from bladder transitional cell carcinoma, were provided by Dr. W. McCombs of the Scott and White Clinic, Temple, Texas. Of the primary transplants, tumor line 13678, a bladder carcinoma, was kindly provided by Dr. D. Paulson and Dr. R. Bonar of Duke University. PaCak-1 (a pancreatic adenocarcinoma), BLT Cak-1 and BLT Cak-2 (transitional cell carcinomas of the urinary bladder), and a breast adenocarcinoma were established from primary transplants. For tumor inoculation, animals were anesthetized with ether or Nembutal. When cultured tumor cell lines were used, 5 x 10^6 viable tumor cells were injected s.c. With tumor lines established from primary transplants, tumors grown in nude mice were removed aseptically, cut to 0.2- x 0.2-cm pieces, and transplanted s.c. Two transplantation sites were selected for this study: (a) the anterior lateral thoracic wall and (b) the posterior lateral aspect of the trunk (lumbar region). Chart 1 shows the exact locations of the transplantation. Tumor volume was measured with calipers by using the formula: length x (width)^2 x 0.4 (1). At various time intervals, tumors were removed and processed for histopathological evaluation. For this purpose, tissue sections were stained with hematoxylin and eosin. Occasional sections were stained with Masson's trichrome and reticulin.

RESULTS

Tumors growing s.c. in the anterior thoracic region showed a faster growth rate as compared to the same tumors transplanted in the posterior aspect of the trunk. The difference in growth rates became apparent as early as the first post-transplantation week and persisted throughout the entire experimental period. Measurements taken at weekly intervals showed a statistically significant difference at all points of measurements taken during the period of active tumor growth (Chart 2). The difference became more pronounced toward the end when anterior tumors continued to grow, whereas tumors growing posteriorly had for all practical purposes remained static. These findings were consistent with all tumor lines studied, as shown in Table 1.

For histopathological evaluation, multiple sections at various tumor levels were studied. It was established that tumors grown anteriorly were better vascularized and characterized by less...
necrosis and fibrosis than were posteriorly grown tumors. Furthermore, infiltration of tumor bed and metastases to regional lymph nodes, a frequent finding in tumors growing anteriorly, were absent when the same tumors were transplanted posteriorly.

Table 2 summarizes the observed regional differences 30 days posttransplantation with regard to growth and histopathology of human tumors grown s.c. in nude mice. An arbitrary scale of "+" to "+++++" was selected in evaluating the intensity of various tumor characteristics.

DISCUSSION

The results of the present study are in agreement with previous reports dealing primarily with i.d. transplantation of mouse tumors to their syngeneic host (2, 3). They further show that regional growth differences are prominent in nude mice receiving a variety of human tumors. In addition, they point out that this phenomenon is independent of the site of origin and histological type of the primary neoplastic growth in humans.

The poorly understood regional differences in growth rates of transplantable tumors have been largely attributed to persistence into adult life of anteroposterior gradient operating during ontogenesis (2). Although this interpretation may be valid, other factors are probably implicated and should be considered in the discussion.

From Table 2 of the presented data, it becomes apparent that blood supply is a key factor influencing tumor biology and its histology. It is beyond doubt that a better vascularized area creates a more favorable milieu for tumor implantation and subsequent growth than do less vascularized regions. We consider this information important in view of the momentum the nude mouse is gaining as a model for testing tumor response to treatment. The region into which the tumor has been transplanted may affect not only its growth rate; it may influence its response to treatment as well. In addition, the slow growth rate of posteriorly growing tumors followed by a period of minimal or even static growth may introduce a certain degree of error and bias interpretation of important experimental data.

It is concluded that biological characteristics of human tumors growing s.c. in nude mice are influenced by the anatomical region into which they grow.


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