Heterogeneity and Prognostic Significance of Macrophages in Human Colonic Carcinomas

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ABSTRACT

Previously, we reported that high concentrations of eosinophils in human colonic carcinomas are associated with better prognoses, that sections taken 1 cm remote from (deep to) the margin of tumor (SRM) and sections contiguous to the margin (SCM) of tumor and adjacent uninvolved colon contain significantly different concentrations of eosinophils, and that concentrations of eosinophils in SCM and SRM are both useful and complementary for the prediction of prognosis. As a first step towards studying the ecology of the eosinophil in colonic carcinoma and with the goal of identifying other kinds of cells that might be useful for the prediction of prognosis, we counted cells in SCM and SRM that expressed histochemically demonstrable acid phosphatase, \( \alpha \)-naphthyl butyrate esterase, and peroxidase. The tumors of patients with and without metastases at the time of resection of the primary tumor contained different \( (P = 0.0314) \) concentrations of cells with histochemically demonstrable \( \alpha \)-naphthyl butyrate esterase in SCM but not in SRM. In contiguous 1- to 2-\( \mu \)m sections, morphologically macrophage-like cells with histochemically demonstrable acid phosphatase and cells with histochemically demonstrable \( \alpha \)-naphthyl butyrate esterase were found to be present in different concentrations both in SCM \( (P < 0.01) \) and in SRM \( (P < 0.01) \); i.e., these phenotypic markers appear to identify different subpopulations of macrophages in tumors. In contrast to our previous study of human pulmonary alveolar macrophages, examination of sections stained sequentially for these phenotypic markers that are commonly used for the identification of macrophages in tumors revealed numerous cells in the same sections that expressed histochemically demonstrable acid phosphatase (red) but not \( \alpha \)-naphthyl butyrate esterase (brown) and vice versa. Several of these markers promise to be useful and complementary for the prediction of prognosis.

INTRODUCTION

The infiltration of tumors by macrophages and other cells traditionally termed "inflammatory" or "host" cells has been the subject of numerous reports for nearly a century (1-5). Such infiltration generally has been associated with a more favorable prognosis in human cancers (1); however, most reports have been either only semiquantitative or totally subjective. Infiltration by macrophages has been associated with a favorable prognosis in studies of human mammary carcinoma (6). Herlyn and Kowalski (7) expressed the view that "macrophages were strongly incriminated as effector cells" in their successful inhibition of the growth of human tumors in nude mice with monoclonal antibodies.

Numerous investigators have observed that macrophages are technically difficult to recognize (numerically underestimated) when sections stained with hematoxylin and eosin are examined (8, 9). In histological sections, many markers have been used to facilitate the quantification of macrophages; these include non-specific esterase (8, 10), acid phosphatase (6, 10), peroxidase (10), lysozyme (10), and many others. The heterogeneity commonly observed in the study of macrophages that infiltrate tumors has been discussed recently (11, 12). In an animal model, several transplantable tumors derived from a single mouse mammary carcinoma were dispersed by Heppner and coworkers; the macrophages were partially purified by velocity sedimentation; and the purified macrophages from different tumors were found to differ markedly with respect to the activities of several enzymes. The data suggested that the different biological behaviors of these different tumors were associated with elevated or depressed levels of particular enzymatic activities in macrophages.

In this investigation, we wished to study the degree to which some of the more commonly used histochemical markers agree; i.e., we wished to know if the word "macrophage" has a common meaning when investigators use different markers to study macrophages in situ in tumors. We also wished to know what, if any, prognostic significance would be attached to the concentration of macrophages and if there might be more than one recognizable subcompartment with respect to the concentration of macrophages in human colonic carcinomas.

MATERIALS AND METHODS

Between April 1981 and November 1982, tissue from 28 almost consecutive colonic carcinomas was obtained from the operating rooms at the University of Alabama at Birmingham Medical Center by the Tissue Procurement Service of the Comprehensive Cancer Center. Two of the 28 patients with TPNs, 3-29-8 and 44-37, were omitted from the study because SCMs did not show attached, normal, colonic epithelium historically, i.e., were technically inadequate. Two additional patients, TPN 47-25 and 34-25, were omitted from the study because two or more enzyme histochemical preparations on glass microscope slides from their material were broken and/or lost during the transportation of our laboratory from the University of Alabama at Birmingham to Case Western Reserve University. One preparation each was broken for the tumors designated TPN 36-38 and TPN 33-41; however, all other preparations were available for these tumors, and they were retained in the study.

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Tissues were obtained as described in detail previously (13). Specimens were placed in 0.9% NaCl solution in an ice bath in the operating room and transported to the Tissue Procurement Laboratory. All sections were cylindrical and were taken with a sharp, stainless steel, custom-made knife made in the shape of a cork borer. Sections were taken from the margin between tumor and contiguous, uninvolved colon to include approximately one-half tumor and one-half uninvolved colon. Other sections were taken 1 cm remote from (deep to) the margin of the tumor. Samples obtained in this fashion were cut with an array of parallel razor blades in an especially fabricated blade holder oriented parallel to the lumen of the colon and perpendicular to the luminal surface of the tumor. The slices of tumor prepared in this manner measured approximately 1 x 5-9 x 5-10 mm. They were placed on a piece of paper and snap-frozen on a thick metal surface in a vapor-phase nitrogen freezer.

Previously, we (14) reported that 1-mm-thick sections that included bronchogenic carcinoma and contiguous lung could be snap-frozen as described above, stored over liquid nitrogen, thawed with gentle agitation in either of two fixatives, embedded in methacrylate, and stained for several histochemically demonstrable enzymes with the techniques described by Beckstead and coworkers (15, 16). In our previous study of pulmonary alveolar macrophages (14), three observers counted 100 pulmonary alveolar macrophages each in 280 sections (28,000 cells x 3 observers or 84,000 cells). With 4,200 cells examined for each enzyme in tissues fixed with paraformaldehyde as described previously (13), the proportions of pulmonary alveolar macrophages with histochemically demonstrable enzymes in sections fixed fresh or fixed after storage over liquid nitrogen were: acid phosphatase, 91.33% and 86.74%; \( \alpha \)-naphthyl butyrate esterase, 84.10% and 81.08%; and peroxidase, 80.12% and 67.76%. While the differences in the proportions of cells with histochemically demonstrable enzymatic activities in tissues fixed fresh or fixed after storage over liquid nitrogen were not significant for acid phosphatase or \( \alpha \)-naphthyl butyrate esterase, they were significant for peroxidase (details are provided in Soufleris et al. (14)). The techniques that we used are modified from those of Beckstead and coworkers (15, 16). The details of the enzyme histochemical stains (14) and the stains for eosinophils (13) were described in detail by us.

The methods that we use for the selection of the particular portion of the tumor to be counted were described in detail previously (13). In brief, under magnification too low to permit one to distinguish individual kinds of stromal cells, a line is etched on the bottom of the microscope slide underlying the longest axis of the tumor. For successive serial sections, we reproduce this line as nearly as possible on successive slides. The observer then focuses on the line with a 10-power objective, centers the tumor to be counted were described in detail previously (13). In brief, the resection of the primary tumor were different with respect to (a) the concentration of tumor-infiltrating eosinophils in SCM (P = 0.0179), (b) the concentration of tumor-infiltrating eosinophils in SRM (P = 0.0320), (c) the concentration of cells with histochemically demonstrable peroxidase (Chart 1) in SRM (P = 0.0296), and (d) the concentration of cells with histochemically demonstrable \( \alpha \)-naphthyl butyrate esterase (Chart 2) in SCM (P = 0.0314). These were the only measured variables that were able to discriminate in a univariate analysis between patients with and without metastases.

A linear discriminant analysis (18) was used to consider all data simultaneously, i.e., age, race, sex, and all examined markers in both subcompartments of the tumors; the quantitative importance of removing each variable in a stepwise fashion is shown in Table 2. Of particular interest, while the concentrations of cells with histochemically demonstrable (a) acid phosphatase in SCM, (b) acid phosphatase in SRM, and (c) peroxidase in SCM and SRM had not permitted one to distinguish among tumors that had and had not metastasized when considered with the univariate analysis, these characteristics were complementary to the other data in making this distinction with the multivariate analysis (Table 2).

The omission of the concentration of eosinophils in SRM resulted in only a slight reduction in the \( r^2 \) value; we would speculate that the small magnitude of this reduction reflects the fact that the concentration of cells with histochemically demonstrable peroxidase in the same sections is retained. Specifically, the 13 tumors with the highest concentrations of eosinophils in SRM included 9 of the 10 tumors with the highest concentrations of cells with histochemically demonstrable peroxidase; i.e., in most cases, the information of prognostic value associated with high concentrations of eosinophils may have been retained despite the elimination of the concentration of eosinophils as a parameter, since most SRM with high concentrations of eosinophils contain high concentrations of cells with histochemically demonstrable peroxidase (Table 1). This is not surprising since eosinophils in bone marrow exhibit histochemically demonstrable peroxidase (15, 16), and the expression of this phenotype may be retained by many eosinophils after they infiltrate tumor. The subsequent elimination of the concentration of cells with histo-
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Table 1
Summary of data

Primary human colonic carcinomas were sectioned 1 cm remote from the margin of tumor and at the margin between tumor and contiguous, uninvolved colon to include approximately 50% tumor and 50% uninvolved colon. Samples from these two locations were embedded in methacrylate. Serial sections, 1–2 μm in thickness, were evaluated with several histochemical markers.

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<th>AP</th>
<th>NBE</th>
<th>PER</th>
<th>Remote from margin (cells/mm²)</th>
<th>Contiguous to margin (cells/mm²)</th>
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<td>13</td>
<td>8</td>
<td>0</td>
<td>400</td>
<td>2</td>
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</table>

¹ TPN, tissue procurement number (a tissue procurement number is given to each tissue received by the Tissue Procurement Laboratory); ARS, age, race, and sex; MT, métastases; EOS, eosinophils; AP, acid phosphatase; NBE, α-naphthyl butyrate esterase; PER, peroxidase.
² Survival: A, alive; D, dead.
³ NS, no slide; glass slide of preparation broken during relocation of laboratory.

Chemically demonstrable peroxidase causes a larger drop in the $r^2$ value.

Our current study of a relatively small number of tumors shows that cells with phenotypic markers commonly used for the identification of macrophages are more concentrated in SCM than in SRM (Table 1); however, if all tumors are included in the evaluation, these differences are not significant (paired t test: acid phosphatase, $P = 0.1145$; α-naphthyl butyrate esterase, $P = 0.4214$; peroxidase, $P = 0.2041$). If one perhaps somewhat arbitrarily considers only tumors with a concentration of at least 200 cells with histochemically demonstrable acid phosphatase per mm² of tumor (Chart 3), the concentrations of these cells in SCM and SRM (Chart 3) are different ($P = 0.0413$).

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DISCUSSION

This is not the first histochemical study of macrophages in human tumors; however, to our knowledge, it is the first such study that (a) has been quantitative, (b) has been carried out in tissue sections that are sufficiently thin to permit the data to be consistent with the assumption that sections are infinitely thin inherent in most commonly used mathematical treatments of morphometric data, and (c) has demonstrated that many macrophages within colonic carcinomas express acid phosphatase without expressing α-naphthyl butyrate esterase and vice versa. In addition, with somewhat more rigorous quantification, we confirmed Nash's (10) observation of higher concentrations of macrophages at the margins than at locations deeper in colonic carcinomas. This observation is particularly interesting in light of the facts that (a) eosinophils, another kind of "inflammatory cells," are present at higher concentrations in tumor topographically remote from the margin and (b) both the concentrations of eosinophils remote from the margin and the concentrations of macrophages in tumor adjacent to the margin are significant predictors of the presence or absence of metastases at the time of resection of the primary tumor. Although we both observed nonspecific esterase activity in epithelial cells of some colonic carcinomas, this did not prevent the quantification of macrophages in our studies as it did in those of Nash. This latter difference is probably due to the improved morphology with 1- to 2-μm sections in methacrylate compared to thicker, cryostat sections.

Markers for macrophages appear to be much more applicable in some systems than in others. In a recent quantification of macrophages lavaged from the peritoneal cavities of unstimulated mice, Ennist and Jones (19) found concordance among several markers of macrophages including histochemically demonstrable α-naphthyl acetate esterase, morphology, the capacity for phagocytosis, and the presence of Fc receptors. This finding was in sharp contrast to that of Mahoney et al. (12) who purified macrophages from transplantable mouse mammary tumors. They found that the capacity for phagocytosis and the presence of Fc receptors correlated nicely; however, with morphological criteria, they counted approximately twice as many macrophages as were identified by Fc receptors and phagocytosis. Many investigators have quantified macrophages in tumors in situ (6, 8) or in suspensions of cells from tumors by measuring single phenotypic markers, i.e., esterase, peroxidase, lysozyme, etc., with the assumption that the majority of macrophages express these markers. We (14) found that 86-90% of human alveolar macrophages exhibited histochemically demonstrable acid phosphatase and nonspecific esterase (demonstrated in parallel with two different substrates). However, it is apparent from the present study that macrophages in human colonic carcinomas are more heterogeneous than pulmonary alveolar macrophages with respect to these phenotypic markers.

The biological significance of infiltrating macrophages in human tumors is still less than completely understood. Human monocyte-derived macrophages exhibited cytotoxicity for malignant cells in vitro after being allowed to adhere to glass; however, similar cells that had been allowed to adhere only to collagen-coated surfaces failed to demonstrate such cytotoxic activity (20). Similarly, human pulmonary alveolar macrophages and macrophages from the pleural cavity were cytotoxic for lung cancer cell lines after the macrophages were purified by adherence to plastic (21). In some cases, the vulnerability of malignant cells to adherent blood mononuclear cells has been enhanced by prior, sublethal exposure of target cells to antineoplastic chemotherapeutic agents (22, 23). Although we do not know the in vivo function of cells with various macrophage markers in colon cancers and it is too early to know if the macrophage markers studied here are related to survival, the concentrations of cells with several "macrophage markers" in primary tumors were useful in distinguishing between patients with and without metastases at the time of resection of their primary tumors.

The potential importance of subcompartments within human tumors has not been studied in great detail. In speculating about the arrangement and functions of cells of the host's response in tumors, Russell et al. (9) listed several potential subcompartments including "the periphery of the tumor . . . , bands of connective tissue that separated lobules of neoplastic cells . . .," or islands of malignant cells with host cells distributed uniformly and in direct contact with malignant cells. Previously, we (13) reported that the concentrations of eosinophils in colonic carcinomas in SRM and SCM were significantly different and comple-

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**Table 2**

<table>
<thead>
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<th>Variables</th>
<th>$r^2$</th>
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</tr>
<tr>
<td>EosC, ApC, NbeC</td>
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<td>EosC, ApC</td>
<td>0.7499</td>
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<tr>
<td>EosC</td>
<td>0.6778</td>
</tr>
</tbody>
</table>

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* Eos, number of eosinophils/mm²; C, section of tumor contiguous to margin; Ap, concentration of cells with histochemically demonstrable acid phosphatase; Nbe, concentration of cells with histochemically demonstrable α-naphthyl butyrate esterase; Per, concentration of cells with histochemically demonstrable peroxidase; R, section of tumor 1 cm remote from the margin.

---

**Chart 3.** Number of cells with histochemically demonstrable (HD) acid phosphatase (AP) per mm² of tumor in sections contiguous to and remote from the margin of colonic carcinoma and uninvolved colon. For tumors that contained more than 200 such cells/mm² of tumor, the concentration of such cells in these two compartments was different ($P = 0.0413$).
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mentary for the prediction of metastases. In this paper, the identification of additional data of prognostic value included the concentration of cells with histochemically demonstrable acid phosphatase in SRM and the concentrations of cells with histochemically demonstrable acid phosphatase, α-naphthyl butyrate esterase, and peroxidase in SCM. The identification of stromal cells with histochemically demonstrable esterase as macrophages seems relatively unambiguous to us. The overwhelming majority of cells with histochemically demonstrable acid phosphatase resembled macrophages morphologically; however, some plasma cells had low levels of histochemically demonstrable acid phosphatase, and a very small proportion of these were not able to be identified with certainty beyond the recognition of their expression of acid phosphatase. The kinds of cells that were responsible for the phenotypic expression of peroxidase in different compartments of the tumor are quite uncertain, since both eosinophils and subpopulations of macrophages express this marker. When only a small portion of the nucleus was present in the section, identification of particular types of cells with histochemically demonstrable peroxidase was often equivocal.

It seems evident that the quantification of subpopulations of inflammatory cells in different subcompartments of human colonic carcinomas can provide data that may be useful in the stratification of patients with different prognoses for clinical trials of different therapeutic approaches. Moreover, both the observed compartmentalization and the phenotypic heterogeneity suggest that different subpopulations of macrophages have different roles in human colonic carcinomas.

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