addition of 7,8-benzoflavone produced the difference spectra shown in Fig. 3. These are opposite in sign to type I curves obtained with aromatase (*8, 15*) and reflect conversion of the heme-iron from a high- to a low-spin state, that is, displacement of androstenedione (*16*). The fact that a low-spin complex is produced indicates that the interaction of 7,8-benzoflavone with the aromatase P-450 is different than that with the hepatic microsomal cytochromes. In the case of aromatase the low-spin nature of the complex suggests the presence of an additional axial ligand to the heme-iron; this ligand could be contributed by an amino acid residue of the protein or by the ether or ketone oxygen atom of 7,8-benzoflavone (*17*).

Graphical analysis of the titration shows that only one class of binding site is detected and that it exhibits an apparent binding constant of 2.0 μM. This spectral dissociation constant is higher than the true dissociation constant for 7,8-benzoflavone because of competition with androstenedione for binding to the enzyme. We interpret this reverse type I spectral change as evidence for the formation of an aromatase–7,8-benzoflavone complex; it is probable that formation of this complex causes inhibition of the enzyme. Similar difference spectra were obtained when enzyme samples were equilibrated with testosterone or when chrysin was used in place of 7,8-benzoflavone.

Two types of interaction of the flavones with the aromatase could result in a competitive binding with respect to the androgen substrates. Flavones might simply compete directly for the substrate binding site on the aromatase; while flavones appear structurally dissimilar from steroids, certain isoflavones have been found to exhibit estrogenic activity (*18*), presumably as a result of binding to the estrogen receptor. Alternatively, there may be a distinct site on the aromatase that accommodates certain flavones and, when occupied, favors an enzyme conformation with decreased substrate affinity; in principle, such a "regulatory" site could also act differently to enhance enzyme activity, as observed with some of the hepatic monooxygenases. It is not yet possible to distinguish between these mechanisms, but additional structure-activity studies may provide further insight.

Estrogens have profound influences on reproduction, development, and behavior. Because of the presence of flavones in human diets and their therapeutic use and because of the many whole-animal experiments in which the effects of flavones have been studied, it is important to learn whether they affect estrogen biosynthesis in vivo.

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Small Cell Carcinoma of the Lung: Macrophage-Specific Antigens Suggest Hemopoietic Stem Cell Origin

Abstract. *Four surface antigens previously recognized only in macrophages are present on human small cell lung carcinoma cells and tumors. Cancerous cells may arise from macrophage precursors in bone marrow, and these precursors migrate to lung to participate in the repair of damaged tissue produced by continuous heavy smoking. The characteristic presence of neuropeptides such as bombesin in small cell carcinoma, when considered along with these findings, presents new possibilities for the role of such peptides in nervous, endocrine, and immune system function.*

Lung cancer is the leading cause of cancer death in the United States, and its incidence is increasing rapidly with an anticipated 100,000 new cases this year (*1*). Approximately 25 percent of all lung carcinomas are of the small cell (SCCL) or oat cell type, and epidemiological studies indicate that the occurrence of SCCL is associated with heavy smoking (*2*). As seen clinically, SCCL is a rapidly progressing disease with widespread and early metastases; the mean survival time for patients with untreated SCCL is 5 to 7 weeks after diagnosis. The treatment consists almost exclusively of high-dose combined chemotherapy which results in an extension of life expectancy to 10 months, but the treatment may result in considerable patient morbidity and occasional mortality (*3*).

Because SCCL is almost always associated with heavy smoking, some investigators have assumed that the primary tumor is of lung origin. Even though SCCL cell lines have been established (*4*) and various biochemical characteristics shared by these cell lines and by tumors obtained at autopsy have been observed, the origin of SCCL remains elusive. The concept that SCCL arises from lung epithelial stem cells of a neuroendocrine nature (*5*) has yet to be substantiated with direct experimental evidence. Moreover, the notion of a lung origin for SCCL is not only incompatible with the observation that 5 percent of

SCCL patients have no apparent pulmonary involvement (*6*) but also offers little explanation for the early, rapid, and widespread dissemination of tumor to extrathoracic sites such as bone marrow, liver, nodes, and brain (*7*).

An alternative hypothesis that explains these facts is that tissue damage caused by long-term heavy smoking elicits a hyperplastic repair response by monocytes or macrophages of bone marrow origin (*8*); these cells eventually become transformed, colonize the lung as well as other sites, and give rise to the disease known as SCCL. We now present evidence to support this hypothesis; specifically, cultured SCCL lines, as well as human tumors, express surface markers previously shown to be present only on macrophages.

A number of cell lines were examined for the presence of surface antigens with the use of a radioisotopic double antibody binding assay in the presence of aggregated human immunoglobulin G (IgG) (legend to Table 1). Cell lines established from patients with SCCL (*4*) and several other types of cell lines were tested for the expression of a variety of markers with a panel of monoclonal antibodies (OKM1, 10, 9, and 8) previously shown to recognize surface antigens restricted to cells of the granulocyte and macrophage series (monocytes, null cells, and some natural killer subtypes) (*9*). These antigens are not present on lymphocytes, thymocytes, or other tissues such as heart, kidney, brain, liver, or lung (*10*). The protein recognized by OKM1 and OKM10 [also termed MAC-1 (*10*)] is known to be the complement receptor C3bi, although functional roles for the biochemically well-characterized proteins recognized by the other antibodies have not yet been deduced.

In both SCCL lines (NCI-H69 and NCI-H128), the amounts of OKM antigens detected were comparable to those found on macrophage cell lines and unfractionated human peripheral blood mononuclear cells (Table 1). As anticipated, the human T cell line 8402 (as well as MOLT-4 and HSB-2) showed no detectable antibody binding when tested in this assay. Furthermore, the continuous human lung tumor lines, which included representatives of alveolar, squamous, and adenocarcinoma histological types, did not bind specific antibodies to these macrophage antigens in experiments conducted simultaneously. Normal fetal lung cells also did not bind these antibodies, suggesting that an increase in binding to the SCCL lines is not simply due to the expression of fetal antigens typical of some cultured tumor lines. Interestingly, HLA-DR, the type II histocompatibility antigen normally expressed by mature macrophages, could not be detected on the SCCL lines with the monoclonal antibody L243 (Becton-Dickinson). In this respect, the phenotype of the cultured SCCL lines resembles the relatively immature macrophage line U937, which is also DR-negative and poorly adherent (*11*).

It was necessary to rule out the possibility that the presence of these characteristic macrophage antigens on SCCL lines is merely an example of phenotypic divergence produced by extended culture in vitro. Cell membranes from a number of frozen tumors and tissues obtained at autopsy were examined for binding by OKM1 and OKM10; these antibodies recognize antigens that are relatively resistant to proteolysis (*9*). The macrophage histiocytic tumor as well as all four small cell tumors examined showed antibody binding (85 to 188 pg per 200 μg of membrane) clearly outside the range (10 to 63 pg per 200 μg) of the human tissue samples (skin melanoma, lung squamous carcinoma, and normal brain) obtained to serve as negative controls (Fig. 1). In contrast to data obtained when intact cells (SK-MES-1 and MOLT-4) were used in the binding assay (Table 1), membranes prepared from the same cells did bind detectable quantities of primary antibody. Despite the occurrence of macrophages in many human tissues, the observation that a nonspecific monoclonal antibody 63Ag8, pooled normal mouse IgG, and other irrelevant antibodies evince binding to all membranes (including those from SCCL tumors) in the range of 10 to 70 pg suggests that the binding detected in this range is nonspecific, that is, via sites unrelated to antibody specificity.

Our results show that SCCL-cultured lines as well as human tumors share several surface antigens previously known only in macrophages. These cell

Table 1. Expression of macrophage surface antigens by SCCL continuous lung cancer cell lines. The human cancer cell lines have been described (*4, 23*). Antigen expression on nonadherent cells (NCI-H69, NCI-H128, U937, monocytes, 8402, and melanoma) was determined by washing cells in the log phase of growth into binding buffer to a final concentration of 10^6 cells per 0.3 ml. Binding buffer consisted of 20 m*M* tris, 0.15*M* NaCl (*p*H 7.4) with 2 percent human serum, heat-aggregated human IgG (0.5 mg/ml), EDTA (1 m*M*), phenylmethylsulfonyl fluoride (PMSF, 50 μg/ml), heparin (1 unit/ml), chymostatin (1 μg/m), 1 percent trasylol, and azide (0.01 percent). Immunoglobulin G (20 mg/ml in tris-NaCl) was aggregated by heating at 60°C for 60 minutes and subsequent centrifugation at 100,000*g* for 15 minutes. Antibodies of the OKM series (mouse IgG isotype) were used at 0.1 μg per reaction, and samples were incubated at 4°C with continuous shaking for 2 hours. Controls containing no primary antibody were included in every experiment for each cell line. The incubation was terminated by centrifugation for 2 minutes at 1000 rev/min (Beckman tabletop microfuge); the supernatant was decanted, and the pellet was resuspended in 0.05 ml of binding buffer (4°C) containing ^{125}I-labeled rabbit antibody to mouse IgG (New England Nuclear) (40,000 count/min) as second antibody and incubated for 30 minutes. Binding was terminated by rapid filtration (Whatman, GF/B glass filters), and cells were washed twice with 10 ml of ice cold buffer. Antigens on adherent cells (A549, PC-3, PC-9, SK-MES-1, Wi38) were detected by incubating 10^6 monolayer cells with OKM antibodies at 0.1 μg per 0.5 ml for 2 hours at 4°C. The incubated cells were washed twice with 1.0 ml of buffer, and a second antibody was added at 100,000 count/min per 0.2 ml. This reaction was stopped at 30 minutes by washing monolayers three times with 5 ml of cold buffer and subsequent solubilization with 0.1*N* NaOH. Other details were as described for nonadherent cells. The determination of antibody binding was calculated as the difference between triplicate samples tested with (total) or without (blank) primary antibody. Total binding was less than 25 percent of the total added isotopically labeled antibody. Variance among replicates was less than 10 percent, and ranges represent determinations of two to five experiments. The limit of detection for this assay was 15 pg (200 count/min), and the specific activity of the second antibody was 7 μCi/μg. N.T., not tested.

Cell lines (*24*)	Antibody binding to macrophage antigens (picograms per 10^6 cells)			
	OKM10	OKM1	OKM8	OKM9
	SCCL			
NCI-H69	181 to 597	137 to 248	149 to 185	55 to 90
NCI-H128	220 to 489	126 to 146	124 to 140	100 to 120
	Macrophage			
U937	245 to 260	173 to 378	240 to 250	120 to 215
Peripheral blood mononuclear cells	200	135	N.T.	N.T.
	Other			
8402, T cell	<15	<15	<15	<15
A549, alveolarcarcinoma	<15	<15	<15	N.T.
PC-3, lung adenocarcinoma	<15	<15	<15	N.T.
SK-MES-1, lung squamouscarcinoma	<15	<15	<15	N.T.
PC-9, lung adenocarcinoma	<15	<15	<15	N.T.
Wi38, embryonic lung	<15	<15	<15	N.T.
SK-MEL-1, melanoma	<15	N.T.	N.T.	N.T.

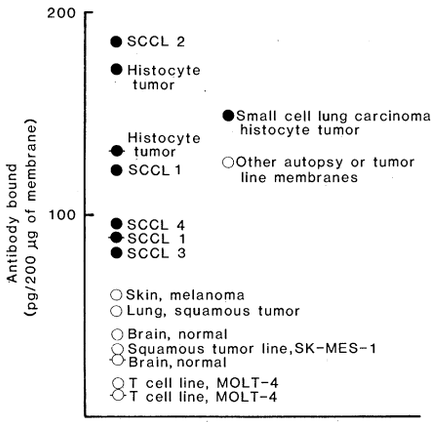

Fig. 1. Expression of OKM1 (–●–, –○–) and OKM10 (●, ○) antigens by SCCL tumors. Membranes from tumors obtained at autopsy and normal tissues were prepared by homogenizing 2 to 5 g of pulverized frozen tissues in 200 ml of 10 m*M* tris (*p*H 8.0), PMSF (50 μg/ml), and EDTA (1 m*M*). When continuous cell lines were used, the cells were homogenized (Dounce) in the same buffer. Membranes were then sedimented (18,000 rev/min for 20 minutes), washed with buffer, and centrifuged again. The sediment was adjusted to 200 mg/ml in 10 m*M* tris (*p*H 8.0), and the membrane fraction was purified further by sucrose gradient centrifugation (50, 30, and 22 percent at 130,000*g* for 2 hours). The fractions at the 30 to 50 percent and 22 to 30 percent interfaces were pooled, adjusted to 5 mg/ml in 0.3*M* sucrose, 50 m*M* tris (*p*H 7.4), PMSF, and EDTA, and stored at −80°C until use. Binding was done on 200 μg per 0.3 ml of membranes as described in the legend to Table 1 except that primary antibody incubations were for 18 hours. All membranes showed a tendency to bind various monoclonal antibodies, presumably by a mechanism unrelated to their combining site specificity because a nonspecific antibody to mouse IgG (63Ag8) as well as pooled normal mouse IgG was bound by all of the membranes tested. Data are the averages (two to four experiments) of the antibody binding (as in Table 1). Values from replicate experiments were within a range of 30 percent, and triplicates within an experiment were within 10 percent. Tumor SCCL 1 was from a liver metastasis (M.M.), SCCL 2 from breast (J.R.), SCCL 3 from skin (J.R.), and SCCL 4 was from lung (Tumor Bank).

surface similarities suggest that small cells are not of lung origin but actually of myeloid or hemopoietic stem cell origin. Our interpretation of the etiology of small cell lung cancer would emphasize lung emphysema and tissue damage (*12, 13*) as a stimulus for myelopoiesis (*14*) and recruitment of precursors derived from bone marrow (*13*) into lung as well as other tissue sites. Continuous heavy smoking, the salient epidemiological feature of SCCL, would provide an ever-present stimulus for monocytic proliferation, and this pool of rapidly dividing immature cells would be potentially sensitive targets for neoplastic transformation. Indeed, the characteristic chromosomal deletion 3p(14-23) of SCCL (*15*) is shared by a large number of hemopoietic tumors (*16*), and chromosome 3 has been suggested to be a key locus mediating hemopoiesis. Disease progression could reflect tumor development within bone marrow with subsequent metastases to secondary lymphatic organs and infiltration into lung and other sites, although alveolar macrophages, Langerhans (*17*), or other marrow-derived cells present in the lung cannot be excluded as the origin of primary tumor.

In addition to suggesting an etiology for SCCL, our findings have other implications connecting recent reports that cells of the immune system secrete and functionally respond to various neuropeptides (*18*). For example, SCCL cells, in addition to their described storage and secretion of bombesin (*19*), will migrate chemotactically to this neuropeptide (*20*), a feature shared by normal human granulocytes and macrophages. Neuropeptides, discretely located throughout the brain and body, have recognized hormone and growth-factor activity (*21*) as well as the ability to mediate mood and behavior. If cells of the nervous and endocrine systems are functionally integrated with the cells of the immune system by networks of neuropeptides and their receptors, this psychoimmunoendocrine (*22*) network should be considered in explaining the pathology of SCCL and other disease states.

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