to adenovirus E1A products or SV40 and polyoma T antigens (*25, 30*). The ability of pX to modulate the activity of other promoters may be important for triggering the sequence of events that lead to leukemogenesis. Since little or no pX protein occurs in fresh leukemic cells from patients, it could be involved in the initiation but not the maintenance of transformation. Alternatively, low levels of pX acting during inappropriate stages in the cell cycle may be enough to maintain the transformed phenotype in the leukemic cell. Availability of vectors producing authentic and mutant pX proteins in animal cells may help answer these questions. Since the name pX implies an unknown function of the gene product, it is no longer adequate. We propose to call this the Ta I protein, for transcriptional activator of the LTR.

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33. We thank M. Satake for help with the immunofluorescence, M. G. Sarngadharan and R. C. Gallo for human patient sera and for discussions, B. Howard and L. Laimonis for CAT vectors, H.-U. Affolter for advice, S. Hughes, D. Hamer, and Y. Ito for discussions and comments, and H. Marusiodis and V. Koogle for editorial assistance. Research sponsored by NCI, DHHS, under contract No. N01-C0-23909 with Litton Bionetics, Inc.

4 April 1985; accepted 1 July 1985

Origin of Human Small Cell Lung Cancer

Ruff and Pert (*1*) describe the presence of antigens (including OKM1) previously believed specific for macrophages on two small cell carcinoma (SCLC) cell lines (originally isolated by us) and four SCLC autopsy specimens. They suggest that SCLC arises from macrophages of bone marrow origin. Although their findings are of interest, we believe that they do not support the conclusions they have reached.

Our own work with 27 SCLC lines indicates that certain "lymphoreticular" antigens detected by monoclonal antibodies can be expressed on SCLC cell lines and tumor tissue samples (*2*). These include the Leu-7 (HNK-1) antigen [present on natural killer (NK) cells] which is found in more than 90 percent of SCLC; Leu M1 (expressed on macrophages and granulocytes); and Leu M2 (present on macrophages). However, certain other NK and macrophage-associated antigens, including Leu 11 and Leu M3, are seldom expressed on SCLC. Specifically, we found the OKM1 antigen on only 8 of 27 SCLC. Of interest, OKM1 was also found on two of five non-SCLC tumors. Thus, our observations based on a much larger sample of tumors only partially confirm their data and actually point to the Leu-7 antigen as a much more frequently expressed lymphoreticular antigen in SCLC. The widespread development of monoclonal antibodies has demonstrated many hitherto unsuspected antigenic relationships between cell groups of diverse function and embryologic origin. For example, cerebellar Purkinje cells express the T-lymphocyte antigen Leu-4 (*3*). The NK cell antigen Leu-7 is also expressed on normal and neuroendocrine cells and tumors, including SCLC (*2, 4*). In addition, SCLC expresses an antigen, lacto-*N*-fucopentaose III, present on other cell types including proximal renal tubules (*5*). Thus, shared antigenicity does not necessarily indicate common lineage or embryologic origin. In addition, Ruff and Pert presented no biochemical evidence that the molecules bearing the shared antigenic determinants on SCLC cells and macrophages are identical.

SCLC cells express many neuroendocrine features (*6*). This phenotype is very similar to that of normal pulmonary endocrine cells, the putative precursor cells of SCLC and bronchial carcinoids (*6*). In contrast, we know of no evidence that macrophages, monocytes, or NK cells express neuronal features. Pearse (*7*) postulated that all neuroendocrine cells have a neuroectodermal origin. However, embryologic studies strongly suggest that the bronchial mucosa is composed entirely of cells of endodermal origin (*6*). Pathologic studies support the notion that SCLC arises in the bronchial mucosa and it expresses morphological and biochemical features of epithelial cells such as desmosomes and the intermediate filament keratin (*6*). Recently, several groups have shown that bronchial mucosal and SCLC cells may demonstrate simultaneous differentiation along endocrine and nonendocrine pathways (*6, 8*). While SCLC selectively expresses certain lymphoreticular antigens, there is much data in support of a unitarian origin for all of the bronchial mucosa and the tumors arising from it, including SCLC (*6*).

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24 September 1984; revised 6 March 1985

Gazdar *et al.* (*1*) take issue with our conclusion (*2*) that SCLC (oat cell carcinoma) arises from hemopoietic stem cells when the normal, macrophage-mediated repair of lung tissue is deranged by continuous heavy smoking. However, we believe that our conclusion stands unrefuted by their comment which cites new evidence that provides support for our suggestion.

Thus, Bunn *et al.* (*3*) have confirmed the presence of one of the four macrophage-specific surface antigens (OKM1) that we described and they have also detected two additional monocyte or granulocyte specific markers (Leu M1, Leu M2) on SCLC lines. The demonstration that Leu-7 can be detected on most SCLC lines (*3, 4*) appears consistent with our hypothesis since natural killer cells are hemopoietic and are believed to be closely related to macrophages. Without obscuring the essential point with the technical issues discussed below (*5*), we emphasize that a total of nine antigens previously detected on hemopoietic cells have now been described on SCLC cells. These markers characterize cells that generate in bone marrow and migrate to other organs, such as lung, guided by chemotactic peptides. Certainly, the presence of multiple monocyte-specific markers on numerous SCLC lines and not on normal lung is not predicted by previous theories of lung carcinogenesis nor is it satisfactorily dismissed by arguments of lineage infidelity.

Surprisingly, Gazdar *et al.* have not considered the emerging and relevant literature [cited in our report (*2*)] showing that cells of the immune system must now be admitted to the group of specialized "neuroendocrine" cells. Indeed, additional clinical evidence documents the ability of monocytes and inflammatory macrophages to produce neuropeptide-secreting neoplasms (*6*). Although attempts have been made to categorize "neuroendocrine" (or APUD, amino precursor uptake and dopamine decarboxylating) cells according to their embryologic origin, by now it seems clear that this is not the relevant criterion since cells of all germinal layers can express neuroendocrine features (*7*). We have emphasized that the presence of short, signal peptides (neuropeptides) and their surface receptors defines this group of cells, whose function is to integrate information from the brain, glands, and immune system and thereby alter the mood and behavior of the whole organism (*8*) via a psychoimmunoendocrine network (*2*). More specifically, our ongoing research shows that bombesin, the neuropeptide known to characterize SCLC lines and tumors, is also concentrated in alveolar macrophages (*9*); bombesin, moreover, induces chemotaxis of both circulating monocytes and SCLC tumor lines by a specific bombesin receptor–mediated process (*10*). Thus, our conclusion of a macrophage origin for SCLC (*2*) can explain not only its surface antigens but also its early and widespread metastasis to neuropeptide-rich body sites (*10*).

Finally, their evidence (*11*) suggesting interconversion between various forms of lung cancer, including the presence of some hemopoietic markers on non-SCLC tumors (*3*), is not incompatible with our theory. Macrophages secrete a plethora of growth factors for local cells which, in pathological states, could potentially give rise to secondary neoplastic foci, resulting in tumors with mixed histology. In this regard, also, bombesin has been reported to be a growth factor for normal bronchial epithelium (*12*). In addition, Langerhans or other dendritic macrophages, having migrated from marrow to take up residence in basal epithelial layers of all body tissues, including lung (*13*), may function as an epidermal stem cell capable of generating the entire spectrum of lung histogenesis (*14*). These resident macrophages may be identical to the poorly understood but morphologically similar neuropeptide-containing cells in lung (variously called Kulchitsky's cells, neuroepithelial bodies, and other) previously proposed to be the origin of SCLC (*15*). Therefore, the presence of high numbers of macrophages participating in tissue repair (such as in smokers' lungs) actually offers an attractive mechanism to explain a common origin for all lung tumors.

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5. Without providing information on quantitative detection thresholds with the various antibodies studied, Bunn *et al.* (*3*) report OKM1 present on 11 of 26 SCLC lines (not eight of 27, as stated by Gazdar *et al.* (*1*)) as well as the other monocyte markers, Leu M1 and Leu M2, present on 20 of 23 and 17 of 20 SCLC lines examined. Thus, a major portion of SCLC lines can be considered to express multiple monocyte-specific antigens. Unlike Gazdar *et al.*, who did not consider the heterogeneity of the normal monocyte population, we would not expect all monocyte markers to be detectable on these cells. The overall pattern of hemopoietic marker expression on SCLC cells seems to define an immature cell of monocytic derivation, since certain markers found on mature macrophages, such as HLA-DR (*2*) and Leu M3 (*3*), are not expressed. Finally, we [like Bunn *et al.* (*3*)] did not perform a biochemical antigen separation; instead, we developed a simple radiochemical antibody-binding assay and showed that it was highly specific by including six negative cell line controls.
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12 June 1985; accepted 28 June 1985