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COMMENTARY

SMALL CELL CANCER OF THE LUNG

THE ROLE OF UNPHYSIOLOGICAL PULMONARY OXYGEN LEVELS

HILDEGARD M. SCHULLER
Laboratory of Experimental Oncology, Department of Pathobiology, College of Veterinary Medicine, University of Tennessee, Knoxville, TN 37901-1071, U.S.A.

Small cell cancer of the lung accounts for about 35% of all lung cancer cases in humans [1, 2] and represents one of the most deadly forms of cancer in general. Metastatic spread to extrapulmonary organs usually starts at an early stage of the disease when the primary tumor in the lung measures just a few millimeters in diameter. By the time pulmonary small cell cancer is diagnosed, metastatic spread is often extensive. Consequently, surgical removal of the tumor is, in most cases, unlikely to result in a cure from the disease. Moreover similar to other solid tumors, small cell cancer of the lung responds poorly to chemotherapy, and the vast majority of patients die within one year of diagnosis.

Regardless of the stage of disease or degree of differentiation, all small cell cancers express a variety of morphological and biochemical features of neuroendocrine function [3]. Among these are the "APUD" [3] characteristics (Amine Precursor Uptake and Dopa-decarboxylase activity), synthesis, storage and secretion of a host of peptide hormones and humoral substances [3–5], expression of neuron specific enolase [6, 7], and the presence of dense-cored secretion granules [8], detectable by electron microscopy and believed to store the peptide hormones.

Small cell cancer of the lung demonstrates a strong epidemiological link with cigarette smoking [1, 2]. In view of this, it seems odd that none of the many noxious agents contained in cigarette smoke induce this cancer type in animal experiments at a significant incidence [9]. Likewise, experimental exposure to smoke itself or a combined treatment with smoke inhalation and chemical carcinogens has failed to induce this lung tumor type at a significant incidence [9–11]. The apparent controversy between the clear-cut etiological association of this cancer type with cigarette smoking in humans and the inability to reproduce this cancer cause-relationship in animals has been the subject of much debate. Explanations for the phenomenon have ranged from "interspecies differences in sensitivity to certain carcinogenic stimuli" to the blunt statement that "cigarette smoking by itself does *not* cause lung cancer". In fact, many scientists have favored the idea that our polluted environment is the "necessary cofactor" missing in experiments where animals are being kept under well controlled (unpolluted) laboratory conditions while exposed to cigarette smoke and/or the chemicals contained in it.

The fact that all small cell cancers of the lung express a variety of neuroendocrine functions has led to the assumption that this tumor type is derived from pulmonary neuroendocrine cells [8]. However, with respect to the well known ability of cells to change from one phenotype into another during the multistage process of tumorigenesis, it seems quite possible that another cell type(s) may be the origin of small cell cancer. In the absence of experimental proof, however, the derivation of pulmonary small cell cancer from pulmonary neuroendocrine cells may serve as a useful working hypothesis for efforts to elucidate the mechanisms that lead to the development of this cancer type.

The most important question to be considered when exploring the potential role of a given cell type as cancer origin is the physiological function of this cell type. Pulmonary neuroendocrine cells may occur as individual cells or in clusters termed "neuroepithelial bodies". They are sparse in healthy adult mammals including humans [12, 13]. They are present, however, in great abundance during the immediate perinatal age period [12, 13], particularly on the first day after birth. Their increase in number is accompanied by significant elevations in the levels of serotonin [13, 14], calcitonin [4, 13] and mammalian bombesin [4, 13]. Moreover, immunocytochemical studies have localized these substances in pulmonary neuroendocrine cells of newborns [12–14]. Based on all this evidence, it has been postulated that pulmonary neuroendocrine cells play an important role in helping the lungs adjust to the transition from the relatively hypoxic intrauterine to the normo-oxic extrauterine life [12–14]. And in fact, when considering that the PO_2 in the pulmonary arteries almost doubles when a mammal takes its first breath, there has to be an extremely fast and efficient mechanism that allows the lung to cope with such a sudden and drastic increase in oxygen levels. Experiments in rabbits and rats have further corroborated this interpretation [14–16]. These experiments have shown that the pulmonary neuroendocrine cells react to significant decreases and increases in pulmonary oxygen levels with an increase in number accompanied by the production and release of vaso-active substances [14–16]. More-

over, it has been shown that this reaction is, in fact, mediated by deviations from normal O_2 levels in the inhaled air and not by deviation in O_2 supply via the bloodstream [17]. These findings, in turn, have lead to the conclusion that *pulmonary neuroendocrine cells can act as chemoreceptors* which "detect" changes in O_2 levels in the inhaled air via receptor-mediated mechanisms [16, 17].

Another important functional aspect of pulmonary neuroendocrine cells is their *metabolic competence*. Pulmonary neuroendocrine cells contain significant levels of the enzymes L-dopa-decarboxylase, prostaglandin synthetase and monoamine oxidase [4], all of which are involved in the metabolism and degradation of endogeneous amines such as serotonin [4, 18]. Both prostaglandin synthetase and monoamine oxidase have been shown to mediate the metabolic activation of a variety of xenobiotics [19–22] such as are contained in cigarette smoke.

The ability of pulmonary neuroendocrine cells for the selective uptake of *simple amines and their precursors* was recognized many years ago [23, 24]. In the case of the endogeneous amine serotonin (5-HT) and its precursor 5-hydroxytryptophan (5-HTP), such uptake is mediated via specific tryptaminergic receptors [18].

Last but not least, pulmonary neuroendocrine cells may *synthetize and release a large variety of peptide hormones and humoral substances* [4, 23]. While some of these products act as vasodilators or vasoconstrictors, others may act as bronchodilators or bronchoconstrictors. With regard to the association of pulmonary neuroendocrine cells with pulmonary small cell cancer, the polypeptide mammalian bombesin deserves particular attention. While the levels of production and release of mammalian bombesin in the lungs of healthy adult mammals are very low or even undetectable, this peptide hormone is the most consistent neuroendocrine marker of small cell cancer and cell lines derived therefrom [3–5]. During the perinatal age period, mammalian bombesin acts as a broncho- and vasoconstrictor, and thus appears to be involved in the mechanisms that allow the lung to adapt to extrauterine conditions. In cell lines derived from pulmonary small cell cancers, mammalian bombesin stimulates cell growth and, therefore, is believed to be a "growth factor" for neuroendocrine cells [25, 26].

The question which logically arises from this summary of functional aspects of pulmonary neuroendocrine cells is: "What significance do all or any of these highly specialized functions have for the mechanisms of induction of small cell cancer?" The only known physiological stimulus that causes a drastic and rapid numerical increase in pulmonary neuroendocrine cells appears to be the sudden and drastic increase of pulmonary oxygen levels resulting from the first inhalation of air after birth [12, 13]. In an effort to exploit this physiological stimulus, we recently conducted an experiment in Syrian golden hamsters [27–29] in collaboration with Dr. H-P. Witschi (University of California, Davis). In this study, the animals were exposed to a constant hyperoxia of 70% O_2 while receiving subcutaneous injections of the carcinogenic *N*-nitrosodiethylamine (DEN) twice per week. Within 8–10 weeks of treatment, the hamsters developed multiple invasively growing lung tumors at a high incidence. Electron microscopy revealed that all tumor cells contained numerous dense-cored cytoplasmic granules, suggestive of neuroendocrine function. At this point, we approached Dr. K. L. Becker (George Washington University, Washington, DC) for help with the identification of potential neuroendocrine markers. Through these collaborative investigations, significant levels of mammalian bombesin, and low but detectable levels of calcitonin and neuron specific enolase, were detected in the tumor cells [28, 29]. In conjunction with the morphological findings, the presence of these three neuroendocrine markers clearly identified the lung tumors induced by hyperoxia and DEN as neuroendocrine tumors. In keeping with our expectation, the simultaneous exposure to the physiological stimulus for neuroendocrine cell proliferation (increase in pulmonary O_2 levels) and the *simple amine* DEN—which these cells in all likelihood are able to metabolize by virtue of their particular enzyme systems—in fact did induce a high incidence of neuroendocrine lung tumors. Hamsters maintained under ambient air conditions and receiving the same dosing regimen of DEN did not develop neuroendocrine lung tumors. In contrast, it has been reproducibly shown that such treatment with DEN under ambient air conditions leads to the development of Clara cell-derived adenomas and adenocarcinomas after a latency period of at least 20 weeks [30, 31]. The simultaneous exposure to hyperoxia while receiving multiple DEN injections hence not only led to a drastic reduction of the tumor latency period in the animals but it also changed the phenotype of the resulting tumors in such a way that neuroendocrine features were expressed. Whether or not these tumors in fact arise from preexisting pulmonary neuroendocrine cells or from one or several other cell types through differentiation is currently the subject of further experiments in our laboratory. Although the fact that neuroendocrine lung tumors can now be experimentally induced at a high incidence is quite spectacular, the underlying mechanisms will require intensive research. Although we currently favor the idea that a "proliferation" of neuroendocrine cells was made possible in our model by the hyperoxia, in a fashion similar to the neonatal mammal, there may be other factors involved. Hyperoxia is well known to have considerable toxic effects on the mammalian lung [32, 33]. Such toxic effects are predominantly found in the lung periphery where endothelial and alveolar type II cells, in particular, may exhibit severe impairment of function [32–34]. This, in turn, may result in a decreased degradation of serotonin in endothelial cells that would lead to elevated levels of serotonin in the lungs. Since serotonin is a substrate for pulmonary neuroendocrine cells, such elevated levels may have direct effects on these cells. Moreover, impaired surfactant production due to toxic effects of the hyperoxia on alveolar type II cells may result in disturbed ventilation of the lung periphery. This, in turn, could potentially stimulate pulmonary neuroendocrine cells.

Regardless of the nature of the mechanism(s) that may be responsible for the induction of neuro-

endocrine lung tumors in our hyperoxia–DEN model, the entire system seems, at first glance, to bear little resemblance to any condition that may prevail in a smoker's lung. And yet, cigarette smokers represent the single best identified group among the human species who consistently develop the most malignant subtype of neuroendocrine lung cancer, namely small cell cancer [1, 2]. As mentioned in the introductory part of this review, experimental hypoxia has also been reported to stimulate the proliferation of pulmonary neuroendocrine cells [16, 17]. Moreover, the reaction of pulmonary neuroendocrine cells to hypoxia is mediated by receptors that apparently detect deviations from physiological O_2 levels in the ventilated air of the lung [17]. The first thing that comes to mind in this context is that carbon monoxide and other constituents of the gas-vapor phase of cigarette smoke may create a relatively hypoxic condition in a smoker's lung. However, considerably more factors may be involved that all lead ultimately to a diminished supply of O_2 to the lung. It is well established that cigarette smoking causes a host of chronic respiratory and cardiovascular diseases [35]. In particular, chronic obstructive lung disease, like chronic bronchitis and emphysema, results in poor ventilation and hence deficient O_2 supply to the affected segments of the lung. But what evidence is there that such diseases cause a "proliferation" of pulmonary neuroendocrine cells? Over the years, a number of articles have been published, all of which indicate that conditions which cause chronic general hypoxia, poor ventilation, or focally impaired ventilation in the lung may be associated with hyperplasia of pulmonary neuroendocrine cells along with increased levels of their endogeneous products or, even, with an increased risk of lung cancer.

Elevated levels of serum and urinary calcitonin levels along with increased numbers of pulmonary neuroendocrine cells have been reported in patients with emphysema, tuberculosis or bacterial pneumonitis [36]. Each of these conditions results in airway obstruction and poor ventilation of the affected lung segments. In keeping with our assumption that such conditions are likely to increase the risk of developing small cell cancer of the lung, a significantly increased "risk for lung cancer" was reported recently in smokers with ventilatory obstruction [37]. In the investigation cited [37], the presence of airway obstruction was even more of an indicator for the subsequent development of lung cancer than was age or the actual level of smoking. Unfortunately, the article (like many other epidemiological studies) does not specify the histological type(s) of the lung cancer cases studied. In view of the hypothesis presented in this review, it would be most desirable if such information would become available through future investigations. It is important to note, however, that, unlike smokers, nonsmokers show only a weak, but significant, association with higher lung cancer risk [37]. One possible explanation for this phenomenon would be that it is important that the exposure to unphysiological pulmonary oxygen levels be simultaneous with exposure to potent respiratory tract carcinogens such as are contained in smoke.

Ionizing radiation and asbestos have both been recognized as factors that increase the risk of pulmonary small cell cancer in smokers [1, 2]. Both conditions *per se* are well known causes of chronic obstructive lung diseases (e.g. pulmonary fibrosis, asbestosis). Again, when linked with simultaneous exposure to cigarette smoke, the incidence of small cell cancer is increased, whereas in nonsmokers the incidence is considerably lower [2]. In keeping with the hypothesis of this review, that a reactive increase in the number and function of pulmonary neuroendocrine cells plays a major role in the induction of neuroendocrine lung cancer under such conditions, experiments in rats demonstrated recently significant increases in the levels of mammalian bombesin and vasoactive intestinal peptide (VIP) in the lungs of animals with chronic asbestosis [38]. Both of these peptides are markers of neuroendocrine cell activity in the lung and other organs [4]. Typically, the elevated peptide levels were not observed during the initial stages of asbestosis development but were restricted to later stages of the disease at which time asbestosis caused obstruction of airway ventilation [38]. Again, this finding supports the theory that impaired ventilation resulting from obstructive disease may trigger a "hyperplasia" of pulmonary neuroendocrine cells.

In a hitherto unreproduced experiment, Blair [39] reported the induction of small cell carcinoma of the lung in 20% of rats treated with intratracheal instillations of benzo[*a*]pyrene and ferric oxide particles. Because Blair's diagnosis was based on histopathology from sections stained with hematoxylin/eosin and were lacking more advanced diagnostic proof, his reports were met with disbelief by the scientific community. In retrospect, it appears that the fairly large ferric oxide particles may have caused obstruction of small airways. This, in turn, may have led to a reactive hyperplasia of pulmonary neuroendocrine cells that could then be transformed into neoplastic cells by the simultaneously administered benzo[*a*]pyrene.

People residing at high altitude reportedly have a significant incidence of the otherwise rare cervical paraganglioma—a neuroendocrine cell-derived neoplasm of the carotid body [40]. Moreover, rabbits living at high altitude over long periods of time demonstrated an increase in the number of pulmonary neuroendocrine cells [41]. In contrast, short-term exposure to hypoxia resulted in decreased numbers or unchanged numbers of pulmonary neuroendocrine cells [42]. Although no epidemiological data are available on this subject, it is to be expected that high altitude residents who smoke are at higher risk than the "average smoker" to develop small cell cancer of the lungs. Likewise, everyone who by profession, disease, or habit is exposed to a general pulmonary hypoxia or impaired pulmonary ventilation is likely to be at higher risk than the average population to develop neuroendocrine lung cancer. As evidenced by our hyperoxia–DEN tumor model, exposure to *hyper*oxia may pose a similar risk. However, in both cases such risk is only significant if there is a simultaneous exposure to carcinogenic stimuli that are capable of transforming the pulmonary neuroendocrine cells abundant under such con-

ditions. In this regard, chemicals that have structural similarities to the endogeneous amines which are the physiological substrate of pulmonary neuroendocrine cells are prime candidates because they may even be absorbed via selective uptake mechanism. Moreover, chemicals that can be metabolically activated by the enzyme systems present in pulmonary neuroendocrine cells may also be potent inducers of neuroendocrine lung tumors under such conditions.

Obviously, it was not just by chance that we selected the *simple amine* DEN as the chemical carcinogen in our hyperoxia experiment. Although experimental proof for this assumption is still forthcoming from some of our ongoing experiments, we are currently exploring the idea that certain carcinogenic nitrosamines may be selectively taken up by pulmonary neuroendocrine cells via receptor-mediated mechanisms similar to the uptake of endogeneous amines. Moreover, *in vitro* studies using well differentiated cell lines derived from human lung neuroendocrine tumors have provided evidence that pulmonary neuroendocrine cells can metabolize DEN via monoamine oxidase and prostaglandin synthetase enzymes [20, 21]. Although such data, which are derived from studies on cancer cell lines, should be interpreted with caution, a recent experiment conducted in our laboratory suggests that similar mechanisms operate in hamsters *in vivo* (unpublished data).

In summary, the data available in published articles, in conjunction with our recent experience with the new hyperoxia–DEN tumor model, strongly suggest that unphysiological pulmonary oxygen levels over an extended period of time may play a key role in the initiation of small cell cancer of the lung. This interpretation also explains the well-known decrease in risk of developing small cell cancer of the lung after cessation of smoking [1]. Although some of the views and interpretations presented in this review are speculative at this point and will require intensive research, it is obvious that a systematic exploration of the role of physiological functions of pulmonary neuroendocrine cells in the cascade of events that results in small cell cancer may provide valuable information on the hitherto unknown mechanisms of development of this tumor category. Such research may also pave the way towards a target-oriented prevention and therapy of this dreadful disease.

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