Does Unilateral DIPNECH Provide Clues to Pathogenesis?

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Pulmonary neuroendocrine cells are typically found either singly or in small clusters, termed neuroepithelial bodies, in the basilar region of the distal bronchiolar epithelium. Neuroendocrine cells contain multiple biologically active neuropeptides and could potentially contribute to diverse physiologic responses, including fibrosis, bronchoconstriction, and cough. In the normal adult lung, neuroendocrine cells are rare. Increased numbers of neuroendocrine cells are found in fetal lung as well as in association with lung injury, including bronchopulmonary dysplasia, cystic fibrosis, and other forms of bronchiectasis. In animal models of airway injury, regeneration of the airway epithelium originates in Clara cell secretory protein expressing cells adjacent to or within neuroepithelial bodies, suggesting a role of the neuroepithelial body in either providing or nurturing multipotent airway epithelial progenitor cells.

A rare syndrome of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), characterized by florid hyperplasia of neuroendocrine cells in the distal airways with obstructive bronchiolitis, was described in 1992.[1] The clinical manifestations of DIPNECH are most typically a chronic cough and dyspnea with an indolent, slowly progressive course; carcinoid tumors are also frequent.[2] The pathologic features of DIPNECH can often be found in carcinoid resection specimens, although the full-blown clinical syndrome is less common.[3,4] The disorder is typically not suspected before lung biopsy but can be presumptively diagnosed in the setting of a compatible clinical history with a high-resolution computed tomography scan revealing air trapping demonstrated by mosaic attenuation, sometimes accompanied by multiple small nodules and airway wall thickening.[5] For unknown reasons, DIPNECH is predominantly found in middle-aged women. Treatment is largely unsuccessful, although there are cases with improvement in cough (and less frequently in pulmonary function testing) after octreotide. No other treatment is known to be effective for DIPNECH.

In this issue of *Journal of Thoracic Oncology*, Irshad et al.[6] describe an unique case of DIPNECH with unilateral involvement radiographically and on transbronchial lung biopsy. These features suggest limited local spread throughout the airways. The patient was treated with pneumonectomy and to date has not recurred on the uninvolved side. The presentation and clinical decision making of this case are fascinating, but can we learn something about DIPNECH from this experiment of nature?

DIPNECH seems to share some features with another orphan disease that affects females, lymphangioleiomyomatosis (LAM). LAM is characterized by progressive cystic lung disease accompanied by proliferation and lymphatic spread of cells with a smooth muscle phenotype, termed LAM cells, renal angiomyolipomas, and uterine myomas.[7] Research in LAM has been fostered by an active advocacy group, the LAM Foundation, and a key clue to the molecular pathogenesis was provided by the finding of LAM, similar to sporadic cases, in patients with tuberous sclerosis. Investigators found that LAM cells in sporadic LAM harbor mutations in the tuberous sclerosis genes, TSC1 and TSC2, whereas other cells are spared this mutation. Thus, sporadic LAM results from a somatic mutation resulting in a clonal population of cells that proliferate and spread through a mechanism of limited metastasis via lymphatics. Analysis of the pathways inhibited by the

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TSC genes has led to the rational design of a clinical trial utilizing an mTOR inhibitor with some success.[8]

This phenomenon of expansion and limited dissemination of a clonal population of cells with a somatic mutation has been documented to also occur within the respiratory epithelium. A patient without lung cancer, but who had multiple premalignant dysplastic lesions, was shown to harbor a subpopulation of epithelial cells with a dominant negative p53 mutation dispersed throughout the airways of both lungs in 1997.[9] More recently, the mutational analysis of airway epithelium distant from adenocarcinomas in resection specimens has demonstrated that common activating epidermal growth factor receptor mutations can frequently be found both in malignant and nonmalignant tissue.[10]

It is tantalizing that several cases of DIPNECH have been reported in patients with features of multiple endocrine neoplasia type I (MEN1).[2,11] The MEN1 gene frequently exhibits loss of function in carcinoid tumors and seems a prime candidate for a somatic mutation affecting neuroendocrine cells in DIPNECH.[12] I speculate that MEN1 or other somatic mutations limited to hyperplastic neuroendocrine cells will eventually be identified in DIPNECH. This information should lead to the rational choice of targeted therapy to treat this orphan disease.

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