Since the first description of pulmonary neuroendocrine cells in the late 1940's, lung biologists have speculated regarding their possible functions. Pulmonary neuroendocrine cells are the first cells in the developing airway epithelium to demonstrate a specialized differentiation, including the expression of dense core vesicles. The contents of these secretory vesicles have begun to be enumerated, enabling the exploration of their function in lung development. Pulmonary neuroendocrine cells frequently contain serotonin, calcitonin, calcitonin gene-related peptide, and gastrin-releasing peptide (GRP), a member of the bombesin-like peptide family. Bombesin-like immunoreactivity is first expressed in the human at eight to ten weeks and peaks in late gestation, whereas GRP mRNA expression peaks during mid gestation (1, 2). In mouse lung development, GRP mRNA expression peaks somewhat later and bombesin like immunoreactivity is difficult to demonstrate (3). The reasons for the discrepancies between mRNA expression and immunohistochemistry are not known, but alterations in immunoreactivity due to peptide processing, storage, and secretion have been postulated. The timing of expression of GRP suggests that it may play a role in late gestational lung growth and surfactant maturation. In support of this hypothesis, Sunday and co-workers demonstrated that exogenous administration of bombesin to pregnant mice accelerated fetal lung growth and maturation (3).

The enzyme neutral endopeptidase (CD10/NEP) inactivates bombesin-like peptides and is expressed in developing mouse and human lung (4, 5). In this issue of *The Journal of Clinical Investigation,* King and collaborators use a neutral endopeptidase inhibitor to potentially raise endogenous bombesin like peptide levels and produce increased lung growth and surfactant maturation (5). Inhibition of this response by a highly specific bombesin antagonist further supports that this effect is mediated by endogenous bombesin-like peptides. However, administration of the bombesin antagonist alone does not inhibit lung growth or maturation, suggesting that, while bombesin-like peptides can accelerate these processes, they may not be strictly necessary for them to occur. Some caution in the interpretation of inhibition studies is warranted. At least three bombesin receptors exist, but the predominant receptor in lung may be a yet undescribed subtype (6–9). Thus, it is possible that a given antagonist may not block all bombesin responses.

It now seems established that increases in either exogenous or endogenous bombesin-like peptides can stimulate lung growth and maturation in late gestation, a finding with possible clinical application. What role these neuropeptides may play in earlier developmental events is less clear. Hoyt and co-workers have demonstrated that those airway epithelial cells closest to clusters of neuroendocrine cells incorporate [^{3}H]thymidine most rapidly, suggesting that neuroendocrine cells may stimulate epithelial growth by the paracrine secretion of a mitogen such as gastrin-releasing peptide (10). Aguayo and colleagues have implicated a role for bombesin-like peptides in lung branching morphogenesis, a process which begins early in development (11).

The signal transduction pathways activated by bombesin-like peptides have received much study. Of particular interest is that signal transduction pathways activated by bombesin and by cell adhesion involving the integrins have a common point of convergence in the phosphorylation of focal adhesion kinase ($p125^{FAK}$), a protein tyrosine kinase which co-localizes with cellular focal adhesions (12). Thus, bombesin-like peptides may interact with intracellular signaling caused by cellular adhesion to the extracellular matrix, a process of known importance in morphogenesis.

The question of what pulmonary neuroendocrine cells do is beginning to be answered. To date, most of the focus has been on one neuropeptide family, the bombesin-like peptides. As additional and new techniques are applied to this question, further roles for pulmonary neuroendocrine cells in lung development will be elucidated.

York E. Miller
Veterans Affairs Medical Center
University of Colorado Health Sciences Center

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