Gly-Asp)-containing peptides inhibited branching of lung rudiments, which suggested involvement of integrin extracellular matrix receptors. Incubation of 11-d-old lung rudiments in the presence of exogenous FN resulted in impairment of lung branching (14 new branching points, compared to more than 20 in controls). Moreover, dissociated cells from 11- and 13-d embryos attached and spread on FN and express α5β1 FN receptors. However, neither the 120-kD FN fragment containing the RGD sequence nor antibodies to this adhesive site in FN affected lung development in vitro (26 branching points). The 65/75 kD carboxyterminal fragment of FN contains the IIICS adhesive site and did not have an effect on branching (35 branching points). In contrast, incubation of the 70-kD aminoterminal FN fragment resulted in significant inhibition of normal in vitro lung development (11 branching points). The 70-kD aminoterminal FN fragment inhibited deposition of FN matrices of cultured fibroblasts.

These findings suggest that FN matrix assembly is critical for in vitro lung development. Work is currently underway to isolate the FN aminoterminal domain “receptor” critical for normal lung development and presumably for wound healing.

REFERENCE

Bombesin May Play a Role in Fetal Lung Growth and Maturation in Utero and in Lung Organ Culture*

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Pulmonary neuroendocrine cells containing bombesin occur in relatively high numbers in human fetal lung.

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We have previously shown that peak levels of gastrin-releasing peptide (GRP) mRNA are expressed during the human fetal midgestational period (wk 20-23). It has long been speculated that GRP, the mammalian homologue of bombesin that is produced by pulmonary neuroendocrine cells, might have a role in promoting lung development.

To test this hypothesis in an animal model, we first determined that the rodent GRP gene is similarly expressed during fetal mouse lung development, with peak mRNA levels occurring on d 17-18 (birth occurs late on d 18). After showing that immunoprecipitable 125I-bombesin does cross the placenta, we administered bombesin intraperitoneally to timed pregnant CD mice from d 14 to d 18. We then assayed fetal lung specimens for growth (total DNA content, total protein, and 3H-dTDR incorporation into nuclear DNA) and lung maturation (total levels of endogenous saturated phosphatidylcholine [SPC], incorporation of 3H-choline into SPC, and ultrastructural evidence of lamellar bodies [LBS]). We found increased growth on d 17 and d 18, as well as augmented biochemical maturation on d 18. Electron microscopy revealed an increased number of LB-containing epithelial cells on both d 17 and d 18 (p<0.001), as well as a greater number of LBS per LB-positive cell only on d 17. All of these effects were dose-dependent, being observed with 10 and 200 mg/kg bombesin in vivo, but not with 1 mg/kg. In both human and mouse fetal lung organ cultures, we observed increased incorporation of 3H-dTDR into DNA and 3H-leucine into protein (consistent with increased growth) as well of 3H-choline into SPC, indicating that bombesins effects on fetal lung might be direct effects. A monoclonal antibody to bombesin not only blocked bombesin-induced increases in choline and thymidine in vitro, but also blocked baseline automaturation in lung organ cultures.

In conclusion, it appears that bombesin and thus pulmonary neuroendocrine cells play a role in promoting normal lung development.