IGF-I: mediator of fibrosis or carcinogenesis?

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In 1998, Rosenfeld and Oh (9) likened insulin-like growth factors (IGFs) in endocrinology to the elephant in the parable of the blind men and the elephant. Since then, IGFs, and especially IGF-I, may have well become the elephant in other disciplines as well due to the numerous effects IGFs can exert in different tissues and cells.

IGF-I is a pleiotropic peptide with tissue- and cell-specific effects. IGF-I exhibits mitogenic, antiapoptotic, and profibrotic effects in a cell-specific manner. Secreted IGF binding proteins (IGFBPs) exert their effects in an IGF-dependent manner via modulation of IGF function and in an IGF-independent manner. Several cell types secrete IGF-I in health and disease. In normal lung tissues, IGF-I is detected in macrophages. However, in idiopathic pulmonary fibrosis, IGF-I is expressed by alveolar and interstitial macrophages, alveolar epithelial cells, and interstitial mesenchymal cells (1, 10), suggesting that IGF-I may contribute to the initiation or propagation of fibrosis.

Interestingly, the report from Frankel et al., one of the current articles in focus (Ref. 3a, see p. L805 in this issue), provides evidence that overexpression of human IGF-I in alveolar type II epithelial cells of mice results in pulmonary adenomatous hyperplasia and spontaneous pulmonary adenoma formation in older animals. The authors also demonstrate that increased IGF-I production neither alters collagen content nor promotes the development of pulmonary fibrosis. Although IGF-I levels are increased in lung tissues of bleomycin-treated mice (7), Frankel et al. show that transgenic pulmonary expression of human IGF-I neither exacerbates nor ameliorates bleomycin-induced lung inflammation or fibrosis. The findings of the authors raise important questions about the role of IGF-I in fibrosis.

Frankel et al. (3a) thoroughly discuss several possible explanations for the inability of IGF-I to cause lung fibrosis in their model: IGFBP-2 or -3 may be masking the effects of IGF-I in bleomycin-treated mice; IGFBP-1, rather than IGF-IA, may be responsible for fibrogenic activity; delivery of IGF-I into airways does not trigger lung fibrosis and thus expression of IGF-I in macrophages may be necessary; and fibrogenesis may well be a multigenic process. The absence of a fibrotic phenotype in transgenic mice may be due to several additional reasons. First, IGF-I may require cofactor(s), such as one or more IGFBPs, to be expressed concomitantly. Second, IGF-I localization to the appropriate compartment may be required. IGF-I induces collagen production and reduces collagenase levels in fibroblasts (4, 5). Thus, targeting IGF-I expression to mesenchymal cells may elicit a fibrotic phenotype, whereas epithelial secretion fails to induce fibrosis. Third, the levels of IGFBPs may not be sufficient for the development of phenotypic differences or the ratio of IGF to IGFBPs may not be optimal. Finally, the profibrotic effects of IGF-I may actually be a function of IGFBPs. This latter possibility is supported by our recent findings on IGFBP-3 and -5 in idiopathic pulmonary fibrosis (8). We have recently demonstrated that IGFBPs (IGFBP-3 and -5) are overexpressed in fibroblasts cultured from explanted lung tissues of idiopathic pulmonary fibrosis patients and that IGFBP-3 and -5 induce a profibrotic phenotype in normal primary adult lung fibroblasts (8).

The tumor growth-promoting properties of IGF-I are likely due to its mitogenic and antiapoptotic effects. The findings of Frankel et al. (3a) are supported by reports of tumors developing in mice overexpressing IGF-I in different organs. In transgenic mice with targeted expression of IGF-I in the mammary glands, 50% of transgenics developed adenocarcinomas at 23 mo of age (6). Targeting of IGF-I to basal epithelial cells of the prostate resulted in hyperplasia at 2–3 mo of age and a 50% incidence of well-differentiated adenocarcinomas at >6 mo of age (3). Expression of IGF-I in interfollicular epidermis increased the propensity for the development of papillomas (2). Together, these studies confirm the role of IGF-I as a tumor progression factor in multistage carcinogenesis. The findings of Frankel et al. emphasize the complexity of the IGF system and raise valid concerns about the risks of growth hormone (an inducer of IGF-I) and/or IGF-I administration in adults. Further studies are necessary to determine the role, if any, of IGF-I in the development of pulmonary fibrosis.

REFERENCES


