PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

'Dutch' vs 'British', an inducible model of IL-13 effects in emphysema

ArticleInfo		
ArticleID	:	1625
ArticleDOI	:	10.1186/rr-2001-68544
ArticleCitationID	:	68544
ArticleSequenceNumber	:	36
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 2001–9–18 Received : 2001–2–21 OnlineDate : 2001–9–18
ArticleCopyright	:	Biomed Central Ltd2001
ArticleGrants	:	
ArticleContext	:	129312211

Christopher O'Brien,[Aff1]
Corresponding Affiliation: Aff1

Aff1 University of Pennsylvania School of Medicine, Philadelphia, USA

Keywords

Anti-proteinase, asthma, emphysema, IL-13, proteinase, transgenic mice

Context

Chronic obstructive pulmonary disease (COPD) encompasses a spectrum of disorders, including chronic bronchitis, small airway disease, and emphysema, whose etiologies are often blurred with that of asthma. The 'Dutch hypothesis' for the development of COPD focuses on the importance of shared endogenous factors and pathways while the 'British hypothesis' emphasizes the importance of exogenous factors (smoke, infections etc.). The specific assessment of factors mediating airway hyperreactivity in asthma and parenchymal destruction in emphysema, using gene knockout and transgenic models has been limited by the inability to tease out developmental effects of gene disruption from adult onset effects. Utilizing a novel transgenic murine model, this study set out to test the hypothesis that Th2 cytokines (interleukin [IL]-13), important in the pathogenesis of asthma, can activate proteolytic pathways that may be relevant in COPD.

Significant findings

The authors utilized a novel, externally regulated (tetracycline-inducible), lung-directed, overexpression transgenic murine model to assess the effects of IL-13 overexpression in adult animals. In this model, adult IL-13 overexpression yielded a phenotype analogous to COPD with enhanced lung volumes and compliance, as well as mucous gland hyperplasia. IL-13 overexpression induced markedly increased expression of select matrix metalloproteinases (MMP -2, -9, -12, -13, -14) and cysteine proteinases (cathepsins B, H, K, S, and L). With inhibition of MMP or cysteine proteinase activity, there is a marked reduction in IL-13-induced lung hyperinflation, increased compliance, and tissue inflammation, but no change in mucous metaplasia and increased mucus production. IL-13 overexpression also resulted in an 80% decrease in a1-antitrypsin expression, an increase in tissue inhibitors of metalloproteinases (TIMP)-1 expression, but no significant effect on expression of other

lung-relevant antiproteinases (TIMP-2, -3, -4, secretory leukocyte protease inhibitor, or cystatin C). In support of a 'Dutch hypothesis' model, the authors concluded that adult overexpression of IL-13 yielded a phenotype similar to subsets of human COPD. These effects yielded substantial alterations of proteinase/anti-proteinase balance (both MMP- and cysteine-proteinase-based) that mediate IL-13-induced lung hyperinflation, increased compliance, and some aspects of inflammation, but not mucous metaplasia and mucus production.

Comments

The unique approach utilized by the authors, using an externally regulable, organ-directed transgenic model system, represents the next generation of transgenic models and provides an important tool in the assessment of adult expression of specific factors in the development of adult-onset pulmonary disease. This approach allowed the discrimination of adult onset processes from the confounding effects of development-dependent abnormalities typical of non-inducible transgenic models. A related article published by the same group examines the effects of overexpression of IFN-? on the induction of emphysema in a mouse model (see Additional information).

Methods

Externally regulated transgenic mouse model of emphysema, bronchoalveolar lavage, lung volume and compliance measurement, immunohistochemistry, ELISA, northern blot, RT-PCR, western blot, zymography, morphometric analysis.

Additional information

Wang Z, Zheng T, Zhu Z, Homer RJ, Riese RJ, Chapman HA, Shapiro SD, Elias JA: **Interferon gamma induction of pulmonary emphysema in the adult murine lung.** *J Exp Med* 2000, **192**:1587-1599.

References

1. Zheng T, Zhu Z, Wang Z, Homer RJ, Ma B, Riese RJ Jr, Chapman HA Jr, Shapiro SD, Elias JA: Inducible targeting of IL-13 to the adult lung causes matrix metalloproteinase- and cathepsin-dependent emphysema. J Clin Invest. 2000, 280: 1081-193.