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Lung alert

Longevity of alveolar macrophages allow sustained in vivo expression of the human α 1-antitrypsin gene and amelioration of emphysema

This study describes the transduction of mouse pulmonary alveolar macrophages using an intratracheally instilled lentiviral vector. The transferred genes were expressed in vivo for the duration of the lifespan of the mouse. Labelling studies using bromodeoxyuridine (BrdU) revealed continued expression of the transgenes by alveolar macrophages present in the mouse lung at the time of infection, and not by those recruited after inoculation.

Using this method, a human α 1-antitrypsin-expressing lentiviral vector (ET1 α hAAT) was instilled into live immunocompetent mice. The result was stable and sustained secretion of human α 1-antitrypsin protein primarily in the lung by alveolar macrophages augmenting murine α 1-antitrypsin levels. A model of emphysema was induced in these mice and in a control group by intratracheal installation of porcine pancreatic elastase. The control group consisted of immunocompetent mice previously infected with a lentiviral-mediated reporter transgene (EF1 α GDP). The effects of elastase on lung compliance, area-weighted mean alveolar diameter (an index of airspace enlargement in emphysema) and its heterogeneity were significantly less in the ET1 α hAAT-expressing mice compared with the EF1 α GDP group (all $p < 0.05$).

This study demonstrates longevity of pulmonary alveolar macrophages in mice, and challenges previously held views that they are short lived. Lentiviral transduction to achieve prolonged therapeutic secretion of human α 1-antitrypsin in vivo may make them a potential target cell population for application of gene therapy.

► **Wilson AA**, Murphy GJ, Hamakawa H, *et al*. Amelioration of emphysema in mice through lentiviral transduction of long-lived pulmonary alveolar macrophages. *J Clin Invest* 2010;**120**:379–89.

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