

Institutionen för Medicin  
Enheten för Lungmedicin  
Karolinska Institutet

# Platelets and Eosinophils in Lung tissue remodelling

av

Ulrika Zagai

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras på svenska språket i Thoraxaulan, N2:U1, Karolinska Universitetssjukhuset, Solna, fredagen den 15 september 2006, kl 9.00



**Handledare:**

Docent Magnus Sköld  
Karolinska Institutet

**Bihandledare:**

Docent Joachim Lundahl  
Karolinska Institutet

**Opponent:**

Docent Bengt Särnstrand  
Lunds Universitet

**Betygsnämnd:**

Docent Christer Jansson, Uppsala Universitet  
Docent Guro Gafvelin, Karolinska Institutet  
Professor Karl Gösta Sundqvist, Karolinska Institutet

Stockholm 2006

## Abstract

Tissue injury and inflammation followed by effective repair restores normal function, but defective repair with associated tissue remodelling and fibrosis can lead to loss of organ function. Thus, interactions between inflammatory and mesenchymal cells in connection with the remodelling processes are of considerable importance with regards to the development of pulmonary disorders, since this interplay determines the outcome of the disease. At present, no clinical treatment for fibrosis is available and it is of considerable importance to improve our knowledge concerning the mechanisms that lead to tissue remodelling and fibrosis in order to develop effective therapeutic strategies. The present thesis was designed to explore the impact of two important inflammatory cells, platelets and eosinophils, on remodelling of lung tissue employing *in vitro* systems.

Data are based on experimental models such as fibroblast-mediated contraction of collagen gels, which reflects the contractile process typical of tissue remodelling. In this model human lung fibroblasts are cultured in an artificial lung tissue consisting of type I collagen. The advantages of such a system are that the cells are allowed to spread in three dimensions as fibroblasts *in vivo* and, furthermore, demonstrate more *in vivo*-like functional properties. To monitor fibroblast recruitment, which is also an important step in the remodelling process, we employed Boyden chambers with type I collagen coated filters.

Platelets and eosinophils were cultured together with fibroblasts in collagen gels to explore the influence of these cells on gel contraction. Both platelets and lysate thereof stimulated fibroblast-mediated contraction of collagen gels and both PDGF and TGF- $\beta$  contributed partially to this effect.

Furthermore, both peripheral blood eosinophils and eosinophil-like differentiated HL-60 clone 15 cells stimulated the fibroblast-mediated collagen gel contraction. ECP was one of the proteins produced by eosinophils involved in this interaction between eosinophils and lung fibroblasts. Moreover, ECP stimulated the release of TGF- $\beta_1$  by both monolayer and three-dimensional cultures of lung fibroblasts. ECP also enhanced the level of TGF- $\beta_1$  mRNA in these lung fibroblasts.

Both media from cultures of peripheral blood eosinophils and ECP (native and recombinant) alone stimulated the migration of lung fibroblasts, effects that were attenuated by neutralising antibodies directed towards ECP.

The present thesis highlights the ways in which platelets and eosinophils can influence fibroblasts and the extracellular matrix *in vitro*. Based on our findings, we propose that platelets and eosinophils participate in tissue remodelling *in vivo*. The results documented here offer some possible explanations and mechanisms with regards to how these inflammatory cells may contribute to defective tissue repair, fibrosis and impaired pulmonary function

**Keywords:** eosinophil, fibroblast, inflammation, lung, platelet, remodelling

**ISBN:** 91-7140-841-X