

Systematic Identification of Proteases and Anti-Proteases in Developing Primary Airway Epithelial Cells by Global Gene Expression

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The balance between proteases (P) and proteases inhibitors (PI) is a key factor in the development of the airway epithelial barrier and determining the response of the epithelium to external stress. In order to identify these molecules systematically we used measurements of global gene expression of normal human tracheal and bronchial epithelial cells. These cells were cultured using air-liquid interface (ALI) techniques to produce an organotypic model of highly differentiated cells that resemble the epithelial layer of the respiratory tract (EpiAirway™, MatTek Corp.). We studied six time points ranging from basal cells to 13 days ALI culture. High quality RNA was extracted for each time point in triplicate and hybridizations to U133 Plus 2.0 chips performed following standard Affymetrix protocols. After normalization and filtering of raw expression data, we used SAM analysis to identify 1431 genes that differed significantly in abundance during differentiation and grouped these by K-means into 9 clusters that shared similar expression patterns. 57 genes had the GO descriptor protease or peptidase or proteinase (P), with or without inhibitor (PI). Ps included carboxypeptidase D and E, cathepsins C, H, O and S, Kallikreins 6, 7, 8 10, 11 and 12, and proteasome subunits A7, B7, B8, B9 and B10. MMP24 was up-regulated and MMP9 down-regulated. C3 was up-regulated and thrombospondin down-regulated. Amongst the PIs, SERPINEA3, B1, B13, B3, B4 and F1 were up-regulated during differentiation, whereas SERPINE1 and E2 were down-regulated from an initial high. Other up-regulated PIs included 3 cystatins (CST3, CSTA, CSTB), SLPI, SKALP SPINK5 and SPINLW1. The results indicate a previously unrecognised complexity of P/PI balance in airway epithelium.

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